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Biosimilars

*Edited by Valderilio Feijó Azevedo
and Robert Moots*



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Published in London, United Kingdom



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<http://dx.doi.org/10.5772/intechopen.87638>

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First published in London, United Kingdom, 2022 by IntechOpen

IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 5 Princes Gate Court, London, SW7 2QJ, United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Biosimilars

Edited by Valderilio Feijó Azevedo and Robert Moots

p. cm.

Print ISBN 978-1-83881-935-4

Online ISBN 978-1-83881-943-9

eBook (PDF) ISBN 978-1-83968-167-7

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Meet the editors



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Preface

We live in an era of great advances in health biotechnology, one of which is the development of biological medicines. These were introduced in the 1980s and have since become important tools in modern medicine. The clinical advances provided by biological medicines have helped clinicians to better manage chronic diseases such as rheumatoid arthritis, spondyloarthritis, psoriasis, diabetes, and Crohn's disease as well as some types of cancer and rare diseases. However, the introduction of biologics has increased health expenditures, greatly affecting the healthcare budgets of both underdeveloped and developed countries. Fortunately, about two decades ago, biosimilars came to the market as more affordable options for patients treated with biologics. As highly similar, equivalent, and less expensive than their reference products, biosimilars have provided competition in the market and have expanded patient access to biological therapies.

Biosimilars are linked to regulatory advances, health policies, market opportunities, and great financial investments from the pharmaceutical industry. Curiously, not only did the robust approval process of biosimilars lead to the great acceptance of such biologic products, but also real-world evidence and data have contributed to reassuring physicians and patients about the efficacy and safety of biosimilars compared to their reference products. Most importantly, health professionals have come to realize how important biosimilars are to the sustainability of health systems.

As the market for biosimilars continues to expand and the number of biosimilar products for each approved biological reference product increases, the likelihood of patients needing to switch from one biosimilar to another, for whatever reason, is also expected to increase. Several real-world scenarios, of a medical and non-medical nature, may lead to cross-switching between biosimilars of the same reference product.

This book reviews and summarizes the most important topics related to biosimilars to help physicians adopt the best approach to treatment decision-making.

We wish you a pleasant and enlightening read!

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Introductory Chapter: Biosimilars - A Regulatory and Clinical Perspective

Valderílio Feijó Azevedo and Robert Moots

1. Introduction

Biologic drugs are large and complex pharmaceuticals whose structure, physicochemical and biochemical characteristics, and manufacturing process have direct influences on their organic activity [1]. Contrary to synthetic molecules, with simpler structures and low molecular weight, which are obtained exclusively by chemical methods, biologics are very heterogeneous, more unstable compounds, with tridimensional structure and high molecular weight (100–1000 times larger than synthetic molecules), obtained through complex methodologies that include the initial production in genetically modified living cell organisms and processing using fermentation and purification methods [2–4].

The development of biologics in the decade of 1980 revolutionized the way physicians treated their patients, especially with diseases for which an effective treatment was not yet available. Notably, biologic medicines have improved the management of disease, ranging from some types of cancer to chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis, and psoriatic arthritis [5]. However, the high cost of biologics also had a direct impact on healthcare budgets around the world and in many countries they are one of the leading costs related to healthcare expenditure [6]. To rein in healthcare expenditure and promote greater population-based access to biological medicines, biosimilars—highly similar, reverse-engineered versions of existing innovator biological medicines and their active ingredients (originator or reference products)—have emerged as less expensive treatment options compared with reference products after their market-exclusivity patents have expired [7, 8].

Of note, other terminologies have also been applied to biosimilars, such as similar biotherapeutic products, bio-comparables, and follow-on biologics, among other terms. The latter are no longer used, and the term biosimilars is globally accepted.

Regulatory agencies worldwide require a different and more complex processes for the approval of biosimilars compared to generics of synthetic molecules. This is based in a complex set of comparability exercises known as biosimilarity exercise [9].

From a regulatory and clinical point of view, globally, a biosimilar must be as safe, pure, potent, and efficacious as the reference product based on a comprehensive comparability process, such that there are no clinically meaningful differences [10, 11]. Across the United States, Europe, and more universally based on the World Health Organization's standards, establishing biosimilarity follows a stringent yet abbreviated regulatory pathway compared with that for an originator biologic [12, 13]. The regulatory pathways are built to define whether the reference product

and the new similar molecule offer sufficient similarity in terms of structure, purity, pharmacological and clinical characteristics. It is well known that even different batches of the same reference product can exhibit minimal differences through time. These minimal changes could have a direct impact on pharmacokinetics (PK) and pharmacodynamics (PD), as well on efficacy and safety, so the similarity exercise must include a batch-to-batch evaluation of biosimilars in comparison with the reference product [14].

In general, only when all the features in the similarity exercise are matched, the approved product can be defined as a biosimilar [15]. In cases when a product claims to have high similarity to a given innovator but has not provided sufficient evidence, according to all the steps of the regulatory pathway for biosimilars, it might be called an intended copy. Other terms such as “biomimic” and “nonregulated biologic” also have been used for those products [16].

2. Regulatory requirements for approval of biosimilars

Regulatory requirements for approval of biosimilars are generally consistent across the WHO, EMA and Health Canada, and the guidelines issued by the FDA [17, 18]. Although minor differences may exist among these guidelines, sometimes with some small differences in terminology, all these agencies require a stepwise approach to establish biosimilarity of a product. These established regulatory pathways include comparative assessments involving analytical, nonclinical, and clinical studies. The EMA has played a global regulatory lead launching the first regulation to require head-to-head comparative studies for structural characterization, functional in vitro assays, pharmacokinetic and pharmacodynamic evaluations, and safety, efficacy, and immunogenicity assessments. Other agencies have followed the EMA in requiring the same head-to-head studies [19].

Biosimilarity is considered when there is the totality of the evidence from all evaluations, with each step supported by the preceding one:

1. First Step: requirement of analytical studies involving several orthogonal techniques to confirm that the biosimilar has a foundation of quality based on structural and functional similarity to the reference product.
2. Second Step: Nonclinical studies demonstrating that the biosimilar agent acts on the same target or physiologic process and has similar toxicity as the reference product.
3. Third Step: This is the crucial element in the evaluation of a biosimilar product. It is a tailored clinical trial program that compares the pharmacokinetics, clinical efficacy and safety, and immunogenicity of the biosimilar with that of the reference product.

3. Clinical trials for biosimilars

Clinical development of a biosimilar requires a rigorous head-to-head comparison with the reference product and scientific reliable data. The main goal is to demonstrate that any difference in efficacy or safety between the reference product and the biosimilar is less than a prespecified margin of clinical equivalence [20, 21].

The choice of a clinical trial design depends on several factors, and the specific design selected for a particular trial should be explicitly justified in the clinical

protocol [21]. The selection of the primary endpoints in terms of efficacy and safety is a multistep process that includes the statistical design of the main study, as well as the calculation of the appropriate sample size to ensure statistical power. The process requires clear understanding of the comparability prespecified margins. According to the WHO, the selected margin should represent the largest difference in efficacy/safety that matters to the clinical practice. By definition, any difference in result contained within the range would have no clinical relevance. The comparability margins for a certain endpoint result from clinical reasoning, being frequently neither well established nor universally accepted. Thus, the choice of the sample size should be well justified by the sponsors of the study, being usually a combination of the opinion of experts and previously published analyses. In general, phase II trials are not required to biosimilars once the dose of the reference product has been previously established. Comparative clinical (phase I and phase III) trial designs for biosimilars are similar to those for any biologic with respect to most-sensitive patient population, sample size, endpoints, and study duration. The trials should be randomized, double-blinded, and adequately powered [20].

Because the goal of a comparative clinical trial is to demonstrate that the proposed biosimilar is equivalent to the reference product, superiority trials are not appropriate. Instead, nonsuperiority trials, including equivalence and noninferiority designs, are most suitable [22]. Although sometimes noninferiority trials can be used, an equivalence study design is preferred to demonstrate that the biosimilar is equivalent to the reference product. The goal in an equivalence trial is to reject the null hypothesis of nonequivalence and accept the alternative that the biosimilar and reference products are equivalent. The trial should determine whether the biosimilar is no worse and not better than the reference product. This accomplishment is achieved using a two-sided test that requires a superior and an inferior margin limit, the prespecified equivalent margins is selected to detect clinically meaningful differences in effectiveness between the biosimilar and reference product at 95% confidence interval [20]. There are cases that a one-sided noninferiority design may be appropriate, although only if justified (for instance, if the reference product has a wide safety margin). Noteworthy a one-sided test does not demonstrate equivalence, just demonstrates that the biosimilar is not inferior to reference product.

Sample size, study duration and different endpoints are other important considerations in the design of a comparative clinical trial. Sample size is the most important factor of the power of a study and may be affected by the equivalence margins and treatment effects. As long as the equivalence margins narrow, the minimum sample size increases at the same time. On the contrary, the larger the equivalent margins, the lower the number of patients required. The disease for which the biosimilar is being studied will influence the duration of the study. In rheumatic autoimmune conditions, because most of them are chronic, the comparative clinical trial should be of sufficient duration so that both beneficial clinical effects and potential adverse effects may be observed and well documented. Commonly the endpoints selection is based on the endpoints used in the clinical trials of the reference product [20, 22].

4. Regulatory scenario in the underdeveloped world

In Latin America, a heterogeneous regulatory landscape, and nonconsistent approval practices for biosimilars creates decision-making challenges for practicing clinicians. Most Latin American countries have adopted guidelines for the approval of biosimilars. However, among several marketed biologics in the region, there are currently a couple of molecules that could be considered true biosimilars, based

on the WHO criteria. On the other hand, there are products called intended copies approved before the update of the regulations and not following the requirements of a specific biosimilarity pathway. Unlike biosimilars, which have proved efficacy and safety by rigorous head-to-head comparative studies and received approval from international regulatory agencies, none of the intended copies underwent head-to-head clinical trials compared with reference product and received approval from the global agencies such as EMA, FDA, or Health Canada. So safety and efficacy of those biomimics are not fully established. There is a considerable effort in the region to harmonize the regulation on biosimilars [23].

A growing number of countries in Asia have established or are establishing regulatory pathways for evaluation and approval of biosimilars. Japan and South Korea released guidelines in 2009 [24], and Singapore and Malaysia have generally followed EMA guidelines. India released official biosimilar guidelines in 2012 [25].

5. Other regulatory and clinical questions on biosimilars: extrapolation of indications and nomenclature

Omnitrope, a growth hormone biosimilar, was the first biosimilar approved in the world, and CT-P13 was the first biosimilar Mab approved. Since the C-P13 approval in South Korea and Europe, a great deal of experience has been accumulated, which has helped to answer important questions, especially regarding the importance of preclinical essays, extrapolation of indications, and establishing the clinical trial (CT) models and the most sensitive populations [26].

Extrapolation of Indications: This topic had been an important regulatory advantage for biosimilars and had a direct impact on costs to the health systems. It involves considering the potential to extrapolate the efficacy and safety data from one already studied condition to the other indications of the reference product, for which the biosimilar was not directly tested [14].

A cost reduction for biosimilars is implied in the possibility of extrapolation of indications, as a result of transitioning from conducting several phase III trials, as is the norm, to only conducting one comparative pivotal trial. The extrapolation of indications has been supported by the WHO under the following conditions:

(1) A sensitive clinical test model is used to detect potential differences between both products; (2) the mechanisms of action and/or the involved receptor in the studied pathology and the extrapolated one are the same; (3) sufficient characterization of safety and immunogenicity of the biosimilar, and there are no unique/additional safety issues expected for the extrapolated indication; (4) rational and convincing arguments that the efficacy findings from the clinical trial can be extrapolated to the other indications [27].

The case of the extrapolation of CT-P13 was initially controversial. As the first mAb biosimilar to receive approval worldwide, this monoclonal antibody opened the doors to further discussions about extrapolation. At first, the Canadian agency did not approve the extrapolation of indications for inflammatory bowel disease (IBD). The rationale behind this decision was based on differences in the fucosylation profile between CT-P13 and the RP, which was related to a diminished binding capacity with FcγRIIIa. This receptor is related to the antibody-dependent cell-mediated cytotoxicity (ADCC), which is an immune response important in IBD pathophysiology. When analyzed through very sensitive *in vitro* models using isolated natural killer cells from the patients with Crohn's disease, this biosimilar showed a reduced ADCC. However, in less-sensitive models with mononuclear cells from peripheral blood or total blood, this difference was no longer significant. The decision of the Canadian agency for the extrapolation of the indication for IBD

was reverted based on postmarketing results showing no additional efficacy/safety problems in Crohn's disease and results of additional physicochemical analysis [28].

In general, to establish the extrapolation of indications, the manufacturer must use the most sensitive population in randomized clinical trials to detect clinically meaningful differences in not only efficacy but also safety and immunogenicity. The most sensitive population must be well defined and is a population with the clinical condition in which the difference of the effect between the reference product and placebo is the highest (the placebo-adjusted efficacy) [29].

The extrapolation of indications has been authorized by regulatory agencies based on the totality of evidence and also evidence gathered through real-life data showing good outcomes in terms of safety and efficacy for all indications approved [29–31].

The nomenclature of biosimilars has a direct influence on the physician's ability to prescribe an intended biologic medicine. Mostly the naming system has a great impact on the pharmacovigilance, traceability, and interchangeability of biosimilars [32]. If a "biosimilar" is not identical to the reference product, it is reasonable to question whether both drugs should be equally named.

The WHO proposes the use of a unique identification code, called the biological qualifier (BQ), to differentiate drugs under the same International Nonproprietary Name (INN). The BQ complements the INN with the addition of four random consonants to identify the manufacturer of the active substance that would be applied to all drug substances of biological medicines, including biosimilars, innovator products, nonglycosylated and glycosylated proteins, and impure mixtures, and complex biologically extracted products, such as heparin or pancreatin, with the exception of vaccines [33]. The FDA followed the recommendations of the WHO using the same suffix strategy [34].

The proposed suffix should be unique; devoid of meaning; composed of four lowercase letters, of which at least three are distinct; nonproprietary; attached to the core name with a hyphen; and free of legal barriers that would restrict its usage. However, in Asia and Latin America, naming policies are heterogeneous so far.

6. Interchangeability of biosimilars

A number of real-world scenarios, of a medical and nonmedical nature, may lead to cross-switching between biosimilars of the same reference product.

At first we must recognize medical switching occurs when one medication is exchanged for another at the physician's discretion [15]. The objective of a medical switch is always to optimize the patient's treatment benefit. This is not the case for a medical cross-switch involving biosimilars.

In specific instances, cross-switching may be medically necessary to address intolerance issues, such as the avoidance of an irritating excipient (citrate-free vs. citrate-containing biosimilars of adalimumab) or a prefilled delivery device for one biosimilar to which a patient exhibits a hypersensitivity (a needle cover containing a derivative of latex versus a latex-free needle shield) [35, 36].

On the contrary, nonmedical switching occurs when a clinically stable patient, whose current therapy is effective and well tolerated, is switched to another therapeutic alternative [37]. This switching or cross-switching is not related to improving efficacy, safety, and/or convenience, but rather it is moved for the purpose of reducing costs or to ensure that the patient has continued access to the same type of drug [38]. Nonmedical cross-switching is, in general, governed by a third party (e.g., a payer who insists that patients align with the particular biosimilar covered by the health-plan drug formulary or based on an employer-plan offering), initiated by a

hospital pharmacist to avert supply-chain issues due to an unreliable manufacturer, or it may be necessary for a traveling or relocating patient whose current biosimilar might not be geographically available [31, 39, 40]. Out-of-pocket expenses, incentives promoted by the payer, copayment, rebates, or fixed reimbursement hospital fees to inpatient day despite the medication used may also influence a decision to cross-switch to another biosimilar version, or alternatively reverse-switch to the reference product when the economic incentives disappear.

Interchangeability is a characteristic between two or more products that indicates that switching these products back and forth represents no additional risk in terms of efficacy or safety to patients when compared with the products alone [41]. It is not clear so far whether the interchangeability of biologics may impact on immunogenicity safety and efficacy. The FDA, for instance, has recently published a draft requiring clinical data supporting interchangeability [41]. This draft includes evidence from at least one prospective clinically controlled study with a sufficient lead-in-period of treatment with the RP, followed by a randomized two-arm period (switching versus nonswitching). The switching arm should have a minimum of three switches with each one crossing over to the alternative product.

On the contrary, the European guidelines do not provide recommendations on interchangeability, which leaves decisions concerning access to the European national regulatory authorities.

In the United States and many European countries, there is already more than one approved biosimilar from the same reference product and the assessment of efficacy and safety equivalence, and the switching data were obtained from comparison studies.

Despite growing evidence, additional data are still needed in order to investigate whether interchangeability is a viable process. A couple of consensus regarding use of biosimilars have been published for some patient groups [42–45].

These recommendations or consensus recognize biosimilars as an opportunity to increase access to expensive therapies and would accept receiving biosimilar treatment once it was prescribed, respecting a shared decision between the physician and the patient. Medical societies in general agree that the decision to switch products should be based on a shared decision between patient and physician [43, 45].

7. Biosimilars in rare diseases: an opportunity

Rare diseases represent a challenge for the modern medicine. The orphan drugs used in the treatment of rare diseases are often associated with high treatment costs. For many health systems, the costs to treat patients with rare diseases are not affordable. For the development of biosimilars to rare diseases, which should reduce costs, there are a number of associated challenges, such as the high costs of obtaining the reference product for manufacturing purposes; the small of batches in order to determine batch-to-batch variability; difficulties in obtaining a large enough population size for phase I and III trials; and in some cases a heterogeneous population with the condition. However, we expect to update this chapter in the next few years as new biosimilars are approved to treat rare diseases, given this is such an important topic to health systems, patients, and the pharma industry [46, 47].

8. Pharmacovigilance

According to the World Health Organization (WHO), pharmacovigilance is defined as the science and activities relating to the detection, evaluation, understanding, and prevention of adverse drug reactions (ADRs) or any other

drug-related problems. A good pharmacovigilance practice requires reporting of all types of suspected reactions, suspected drug–drug or drug–food interactions, ADRs associated with drug withdrawal, medication errors or overdose, and lack of efficacy to regulatory authorities. Moreover, pharmacovigilance also requires aggregate reports, such as periodic safety update reports (PSURs) and risk management plans (RMPs) [48].

Theoretically, the biological effects of biosimilars in terms of efficacy and safety may differ from those of innovator compounds because of the differences in their manufacturing process, which could cause structural variations and impact on their stability. Moreover, the parenteral nature of the biosimilar agents could also affect their immunogenicity. These clinically important differences highlight that pharmacovigilance of biosimilar compounds is equally necessary as for innovator compounds.

As discussed previously, biosimilar compounds do not have to undergo the same clinical development processes as biooriginators and usually omit the phase II trials. This shortened clinical development process may require greater post-marketing vigilance [49]. Other implications for pharmacovigilance as immunogenicity for the same compound differ in patients with different diseases for various reasons such as route of administration of the drug, concomitant medicine use, and disease indication. Therefore, pharmacovigilance strategies for biosimilars need to be as robust as those for the reference products. Additionally, healthcare professionals play a key part in improving pharmacovigilance through accurate reporting and recording of ADRs [50].

In developing countries, healthcare is often fragmented, with limited financial resources for pharmacovigilance systems. There is also a lack of awareness among physicians about accurate reporting, which may contribute to under-reporting of ADRs [32].

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Biosimilars in Inflammatory Bowel Diseases: General Concepts and Clinical Implications

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Abstract

The treatment of inflammatory bowel disease (IBD) has changed over time with the increasing use of biologics to achieve therapeutic goals. As a result, the cost of treatment increased considerably, making it necessary to develop strategies that could increase access to biological therapies. In this scenario, the biosimilars were developed with the aim of reducing costs, maintaining safety and efficacy compared to the originator. Initially, its use in IBD was based on the extrapolation of studies in other specialties, such as rheumatology. More recently, studies in inflammatory bowel disease have emerged, with favorable results for its use. It is known that there are still knowledge gaps in the use of biosimilars and more experience is needed to increase clinicians' confidence in their clinical practice. This chapter proposes a review of what is currently known about biosimilars in IBD. It discusses about aspects such as safety, efficacy, interchangeability, immunogenicity and switches.

Keywords: treatment, inflammatory bowel disease, biological therapies, biosimilar, the originator, safety, efficacy, interchangeability, immunogenicity, switch, adverse effects

1. Introduction

Biologic therapies, notably the monoclonal antibodies, changed dramatically the scenario of inflammatory bowel diseases (IBD) treatment in the past years. However, such medications have high costs that can limit patient's access to them [1–3]. In 2016, monoclonal antibodies represented only 1% of all biologic medications distributed by the Brazilian Public Health System, but 32% of expenses in biologic products [4]. Additionally, evolving treatment goals for IBD patients aiming deep remission and mucosal healing increased the use of biologics in treatment algorithms [5]. As demand becomes greater and the patents of older biologic therapies are expiring, the interest in marketing comparable versions of the reference products (RP) also increases.

Biosimilars are biologic medications resembling the RP, without clinically significant differences in safety and efficacy. Biosimilars have the potential to expand access to

biological therapies due to price competition and cost savings [1–3]. An analysis elaborated by the Johns Hopkins Bloomberg School of Public Health found that biosimilar price represented 68% of the RP price for infliximab in 2018 in the US and estimated a saving of \$407 million to up to \$1.4 billion in the same year if full biosimilar substitution of infliximab was supported by all employers who self-insure health coverage [6].

Following the expiration of Remicade® patent, CT-P13 was the first infliximab biosimilar to be approved by European Medicine Agencies (EMA) in 2013 after two clinical trials. The studies PLANETAS and PLANETRA compared CT-P13 to the RP in patients with ankylosing spondylitis and rheumatoid arthritis, respectively [7, 8]. In April 2015, the Brazilian Health Regulatory Agency (ANVISA) approved the first biosimilar of infliximab, Remsima® (Celltrion) [9] and, since then, there are three infliximab and three adalimumab biosimilars approved in Brazil (AMGEVITA™, HYRYMOZ® and Xilbrilada®). **Tables 1** and **2** summarize all approved biosimilars from infliximab and adalimumab by FDA, EMA and ANVISA.

This chapter explores general concepts of biosimilars and their implications in clinical practice in the context of inflammatory bowel diseases (IBD) treatment. We aim to summarize the positions of various scientific associations in the IBD field with respect to biosimilars and provide real-life data regarding their effectiveness and safety in countries where they have been used. In addition, the authors will focus on relevant questions encountered in the clinic, including issues related to switch, biosimilar knowledge among IBD specialists and nocebo effect.

Non-proprietary name (NPN) (US)	US	EU	Brazil	Marketing authorization holder (MAH)	Investigational medicinal product (IMP)
adalimumab-atto	Amjevita	Amgevita*	Amgevita*	Amgen	ABP501
adalimumab-adbm	Cyltezo	—	—	Boehringer Ingelheim	BI695501
adalimumab-adaz	Hyrimoz	Hyrimoz*	Hyrimoz*	Sandoz	GP2017
adalimumab-bwwd	Hadlima	Imraldi*	—	Samsung Bioepis	SB5
adalimumab-fkjp	Hulio	Hulio*	—	Mylan	FKB327
adalimumab-afzb	Abrilada	Amsparity	Xilbrilada	Pfizer/Wyeth	PF-06410293
—	—	Idacio*	Idacio	Fresenius Kabi	MSB11022

Marketed.

Table 1.

Biosimilars for adalimumab approved by health authority. Correct of February 2021.

Non-proprietary name (NPN) (US)	US	EU	Brazil	Marketing authorization holder (MAH)	Investigational medicinal product (IMP)
infliximab-abda	Renflexis*	Flixabi*	Renflexis	Samsung	SB2
infliximab-qbtx	Ixifi	Zessly ¹ *	Xilfya*	Pfizer/Sandoz ¹	PF-06438179
infliximab-axxq	Avsola*	—	Avsola	Amgen	ABP710
infliximab-dyyb	Inflectra*	Remsima/ Inflectra*	Remsima*	Celltrion	CT-P13

¹Licensed by Sandoz in EU.

Marketed.

Table 2.

Biosimilars for infliximab approved by health authority. Correct of February 2021.

2. Effectiveness and safety of biosimilars in IBD patients

Biosimilar uptake is increasing worldwide and accumulating evidence has been demonstrating the efficacy and safety of these drugs for the treatment of IBD patients [10–16]. **Figure 1** illustrates biosimilars for infliximab and adalimumab in the pipeline.

However, most data on biosimilars in IBD originate from real-life experience after switching from a reference biologic to a biosimilar [17] and the available randomized controlled studies comparing the reference biologic and biosimilars often had a short-term follow-up [18].

Ye et al. conducted the first randomized, multicenter, double-blind, phase 3 and non-inferiority study evaluating the efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease (CD). Patients were randomly assigned (1:1:1:1) to receive CT-P13 then CT-P13, CT-P13 then infliximab, infliximab then infliximab or infliximab then CT-P13, with switching occurring at week 30. The primary endpoint was the proportion of patients with a decrease of 70 points or more in the Crohn's Disease Activity Index (CDAI) at week 6. Response rates were similar between the two groups (CT-P13: 69.4%, CI 95%: 59.9–77.8 vs. IFX: 74.3%, CI 95%: 65.1–82.2), establishing the non-inferiority of CT-P13 in relation to IFX [18]. Accordingly, in a prospective, observational and multicentre study, Gecse et al. evaluated the efficacy, safety and immunogenicity of CT-P13 in the treatment of CD induction ($n = 126$) and ulcerative colitis (UC- $n = 84$). Remission, clinical and biochemical response were assessed at week 14, corticosteroid-free clinical remission at week 30 and therapeutic drug level was monitored. After 14 weeks of treatment, 81.4% of patients with CD and 77.6% of patients with UC presented clinical response and 53.6% of patients with CD and 58.6% of those with UC achieved clinical remission, according to the CDAI and partial Mayo score. The rates of clinical remission were higher in patients not previously exposed to IFX. Infusion reactions and serious adverse events occurred in 6.6% of patients with CD and 5.7% of patients with UC. The authors concluded that CT-P13 is safe and effective in inducing remission and clinical response in both CD and UC [19].

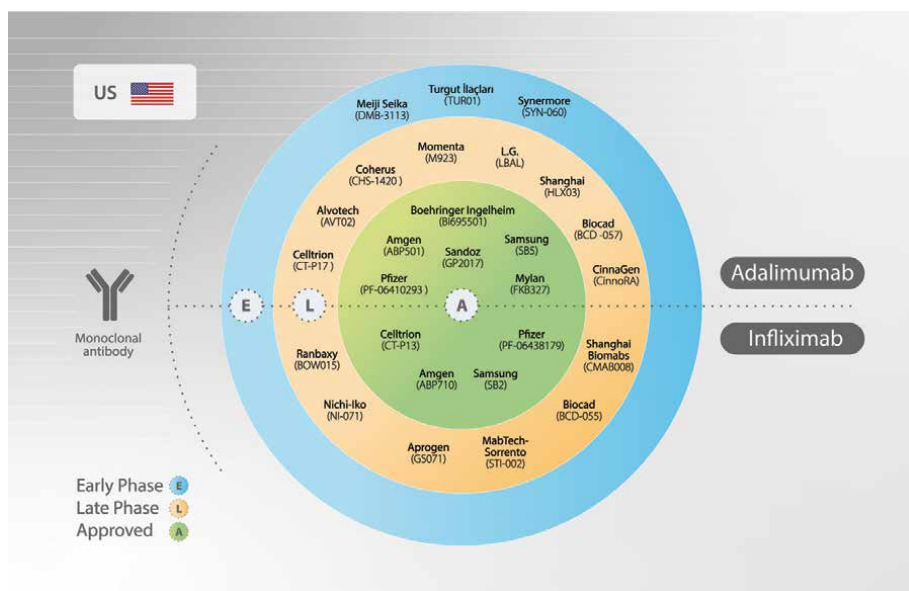


Figure 1.
 Biosimilars for infliximab and adalimumab.

A recent systematic review and meta-analysis by Queiroz et al. assessed the risk and reasons for drug discontinuation in the IBD population that switched from the originator to biosimilars in real-world studies [20]. A total of 30 observational studies comprising 3594 IBD patients who switched from originator biologics to biosimilar with a mean follow-up period over 6 months and a mean duration of treatment with the originator reported as over 1 year were included. In addition, the reasons for treatment discontinuation were extracted and meta-analyzed. The discontinuation rates after a switch were 8, 14 and 21% after 6, 12, and 24 months, respectively. The main reasons for discontinuation were as follows: increased loss of response (2%), remission (4%), loss of adherence (4%), adverse effects (5%) and loss of response (7%). Quality of evidence varied from low to very low depending on the analyzed outcome. The nocebo effect was explicitly analyzed as a reason for discontinuation in only one study [21], and the frequency of reported subjective adverse events was low. It is important to emphasize that most of the studies included in this review did not disclose important information that could have influenced the results, such as disease activity at the moment of switch and drug trough levels before and after switch. This study raises awareness for the urgent need to conducting prospective studies evaluating long-term outcomes associated with the switch of biological therapy in IBD patients.

3. Position statements from different IBD societies (CCFA, ECCO, GEDIIB)

In 2015, a task force of three Brazilian medical societies involved in the treatment of immune-mediated diseases (gastroenterology, rheumatology and dermatology) has first issued guidance on the utilization of biosimilars [22]. Since the approval of CT-P13 in Brazil, several IBD societies worldwide have issued position statements regarding the use of biosimilars for the treatment of Crohn's disease and ulcerative colitis [22–26]. What is still a huge discussion in the medical literature, indeed, is the switch or transition between biologicals: innovator to biosimilar, biosimilar to innovator and biosimilar to other biosimilar. The main recommendations from different IBD societies are summarized as follows:

- a. GEDIIB (Grupo Brasileiro da Doença Inflamatória Intestinal do Brasil): The Brazilian IBD Study Group advises all members about the entry of biosimilars into the Brazilian pharmaceutical market. The guidelines highlighted some important points regarding the switch between biological drugs, which must be carried out with the consent of both the attending physician and the patient [24]. GEDIIB also acknowledge the effectiveness and safety of the biosimilar used in naïve patients as well as in situations of a single switch (original to biosimilar or vice versa).

In fact, what is not clear so far is the ideal time for this switch. Considering switch from biologicals innovator to biosimilar, GEDIIB acknowledges the following:

1. We should not switch if clinical response was not achieved with the initial biological therapy.
2. Before switching, patient must be stable on clinical remission based on clinical, laboratorial and endoscopic data.
3. There should be no suspicion or report of any immunogenicity reaction with the initial biological therapy before switching.

- b. ECCO (European Crohn's and Colitis Organization): In 2017, ECCO have published a positioning statement regarding biosimilars. All other European IBD societies follow the same ideas of ECCO [25]:
1. Once a biosimilar is registered in the European Union by the EMA (European Medical Agency), this product should be considered efficacious and safe to be used.
 2. ECCO acknowledges that biosimilarity is better characterized by performing suitable *in vitro* assays than clinical studies. Moreover, clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. On the other hand, demonstration of safety of biosimilars requires large observational studies, which may be achieved by registries provided by all players somehow involved in the treatment of IBD patients: healthcare professionals, patients' associations and pharma industry.
 3. ECCO also acknowledges transitioning from the originator to a biosimilar in IBD patients. Observational switching studies can provide valuable evidence concerning safety and efficacy. Scientific and clinical evidence is still lacking regarding reverse switching, multiple switching and cross-switching among biosimilars in IBD patients.
 4. It is consensus between the main societies that switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.
- c. CCFA (Crohn's and Colitis Foundation of America) is a professional organization for those physicians, nurses, scientists and other health providers who care for IBD patients in United States. CCFA support all decision of the Food and Drug Administration (FDA) regarding biosimilar approval and its role in ensuring safety of patients. CCFA also acknowledges that all biologicals, innovator or biosimilar should undergo through human testing and meet the highest safety standards. Considering interchangeability, CCFA urges the FDA to provide reasonable proof that switching from originator to the biosimilar would not incur in immunogenicity or loss of response to the innovator, and vice versa.

In summary, IBD societies (ECCO, GEDIIB and CCFA) support a single transition between biologicals, as long as the patients are on clinical remission. Moreover, CCFA believes that when any transition occurs, both patient and physician must be informed of the exact drug the patient is receiving. In agreement with other societies, CCFA does not support multiple switches due to lack of clinical and scientific evidence [26].

4. Different scenarios: double switch, cross switch, switch back

4.1 Overview of interchangeability

Nowadays, what is really being discussed at the medical literature is interchangeability between biological products. The American FDA defined that

interchangeability is when the product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between a candidate interchangeable biologic and its reference product should be evaluated by a clinical study specifically designed for these endpoints [27, 28]. Once approved by FDA's high standards, an interchangeable biologic may be substituted by biosimilar or vice versa, without any involvement of the prescriber [27, 28].

On the other hand, EMA has reported a totally different definition regarding interchangeability of biologics. For the European group, FDA's perception of interchangeability is based in the American legislation and corresponds to an automatic substitution by the European agency terminology. Biosimilars are copy versions of an already existing biological product and approved by a regulatory agency. Then, it is expected to be a high-quality product, efficacious and safe. Because of the high similarity to the innovator, EMA believes that there is no reason for the immune system of the treating patients to respond differently than when the same patient was exposed to the innovator product. That is why EMA advocates that interchangeability is not a legal but a scientific and medical term. Once approved as a biosimilar, it can be interchangeable. EMA regulators stated that they have no intention to create a new legal regulatory requirement for interchangeability of biologics. Indeed, European regulators believe that this dichotomy would create two classes of biosimilars: the interchangeable (approved after being evaluated in a clinical trial specifically designed as required by FDA) and those not interchangeable [28, 29].

In Brazil, so far, health authorities did not issue any specific regulation regarding interchangeability of biological products. A technical note published by ANVISA in October 2018 concluded that interchangeability and substitution are more directly related to clinical practice than to regulatory status. Moreover, ANVISA believes that interchangeability and substitution involve broader aspects, such as specific studies conducted by companies, data from the literature, medical evaluation in each case and cost-effectiveness. Moreover, the Brazilian agency also reported the importance of a medical evaluation and adequate pharmaceutical care in the case of switching from an innovator to a biosimilar. ANVISA also believes that multiple exchanges between biosimilar products and the comparator biological product are not suitable, and traceability and monitoring of use are very difficult in these cases. In fact, ANVISA gave to both, the prescriber physician and the Brazilian Ministry of Health, power to decide about switching between biological products [30]. However, without any recommendation and regulation, unusual scenarios of multiple switches may occur and the appropriate pharmacovigilance will be impaired, compromising the safety of the treatment.

4.2 Single switch

Since the approval of the first monoclonal antibody biosimilar, CT-P13, by the EMA, several observational studies reported the effectiveness and safety of a single switch between a biologic reference and a biosimilar in the IBD's treatment scenario [31]. Others have reported a significant cost savings with the treatment after incorporating biosimilar in the medical practice. On the basis of these findings, it would be likely that switching to biosimilars would no longer be an option but the routine approach for patients who are candidates for biological drugs [32, 33]. However, it has been observed at the literature some problems regarding switching from originator to biosimilars. Chaparro and colleagues in Spain reported a series with almost 200 IBD patients who switch from infliximab reference to CT-P13 and

compared the results to patients kept on the originator. Authors observed higher rates of relapse on the switching group. The cumulative incidence of relapse was 2% at 6 months and 10% at 24 months. In the multivariate analysis, the switch to CT-P13 was associated with a higher risk of relapse (HR = 3.5, 95% confidence interval [CI] = 2–6) [34]. A recent systematic review and meta-analysis by Queiroz et al. reported that discontinuation rates following a switch to a biosimilar in patients with IBD increase over time [20]. Moreover, not long ago, a study by IQVIA analyzed a very large database of German patients with immuno-mediated diseases treated with biologics, which includes ~60% of all prescriptions reimbursed by statutory health insurance funds in Germany [35]. Approximately 30% of patients switched back from an etanercept/infliximab biosimilar to an etanercept/infliximab reference product within 12 months after the initial biosimilar therapy. The authors found no significant effect of different factors, such as age, gender, physician specialty and concomitant therapy [35]. It was speculated by the academic community that discontinuation of the treatment may occur due to a nocebo effect.

Recent studies have assessed the safety and effectiveness of switching to other infliximab biosimilars that became available after CT-P13 and to adalimumab biosimilar. A prospective and observational Germany cohort study described the 80-week follow-up of 144 patients with inflammatory bowel disease after switching from infliximab to a biosimilar (SB2). The same recommendations for the use of infliximab were maintained for the new drug. All patients received infliximab induction and the time to switch to the biosimilar was variable (the mean duration of previous infliximab therapy was 30 months). Most patients were in remission at the time of switch, 36% had mild to moderate clinical activity and none had severe activity. Despite the limitations of the study, it was observed that the disease activity was not affected by the transition to biosimilar, the switching was not associated with lack of effectiveness and was well tolerated [36].

An observational cohort study included 481 patients treated with SB5 (Sb5-switch cohort and SB5-start cohort) over 12 months of follow-up. The biosimilar was effective and safe. The observed rates of primary non-response and secondary loss of response in the switched cohort were similar to those previously reported to the originator [37].

4.3 Reverse, cross-switch and multiple switches

Reverse, multiple and cross-switches will be a challenge for the next years to come. It has been incorporated in clinical practice the need to switch from an originator to a biosimilar. Moreover, some new demanding situations already have come to the biosimilar era. We clinicians now face not only a single switch but also the switch in the opposite direction, for instance, when relapse or adverse effect are observed after a switch between biologics. Furthermore, we will face, in the next months or years, multiple switches among different molecules from one biosimilar to another—named cross-switch. However, we do not have strong evidence to support this new kind of switches. Few observational studies have been reported so far. Ilias and co-authors analyzed 174 patients with Crohn and ulcerative colitis in maintenance therapy with CT-P13 who switched back to reference infliximab due to reimbursement policies in Hungary. No significant changes were observed in remission, trough levels or antidrug antibodies in patients switched from the biosimilar to remicade. No new safety signals were detected [38].

For the very first time, an Italian group has reported multiple switches in IBD. The Sicilian Network for Inflammatory Bowel Disease group analyzed almost 230 patients: 127 (46.0%) were naïve to IFX and naïve to anti-TNFs, 65 (23.5%) were naïve to infliximab and previously exposed to anti-TNFs, 17 (6.2%) were switched

from an infliximab reference to a biosimilar (SB2), 43 (15.6%) were switched from the biosimilar CT-P13 to SB2 and 24 (8.7%) were multiply switched (from infliximab reference to CT-P13 and to SB2) [39]. They observed 67 serious adverse in 57 patients (20.7%; incidence rate: 36.7 per 100 patient-year) and 31 of these events lead to withdrawal. The effectiveness after 8 weeks of treatment was evaluated in patients naïve to IFX ($n = 192$): 110 patients (57.3%) had steroid-free remission, while 56 patients had no response (29.2%). At the end of follow-up, 26.1% interrupted the treatment, without any significant differences in treatment persistency, (log-rank $P = 0.15$). Finally, results of 52 IBD patients who double switch was compared with those of 66 IBD patients switched from originator to CT-P13 (infliximab reference to CT-P13 and then to SB2). Almost 50% of them were in clinical remission in the double switch group after a median follow-up of 40 weeks and only six adverse effects occurred, which lead to discontinuation in three cases (6%) [40].

A prospective multicenter cohort study evaluated the effectiveness and safety of multiple switches in inflammatory bowel disease. One hundred and seventy-six patients were included and divided into three groups (Originator to CT-P13, CT-P13 to SB2 and Originator to CT-P13). Patients had variable previous duration of IFX exposure before index switch (minimum median of 1.9 years), mostly in clinical remission. The dose and interval were maintained after the switch and were only modified if clinically necessary. Similar rates of clinical and biochemical remission were observed in the three groups at 12 months after the most recent switch. Increased immunogenicity was not observed after multiple successive switches [41].

A Dutch multicenter retrospective study assessed the need for reverse switch to infliximab among patients with inflammatory bowel disease using biosimilars (CT-P13). Among 758 patients who switched to CT-P13 after median of 4.7 years of treatment with originator, reverse switching was observed in almost 10% of patients mainly due to gastrointestinal and dermatological symptoms. In nine patients, the reason for switching was loss of response. No relevant differences in pharmacokinetics or immunogenicity were observed. Reverse switching was beneficial in 73.3% of patients and may be considered in case of loss of response or adverse effects following an initial switch [42].

As the reader may see, we just have few reports regarding multiple switches and cross-switch reported in the literature. Further experience in different scenarios will certainly fill in the knowledge gaps and pave the way to increase clinicians' confidence in their clinical practice.

5. Nocebo effect in IBD

Almost one decade after the first approval of a monoclonal antibody biosimilar by the EMA in 2013 [43], an underestimated phenomenon has been observed in patients treated with biological drugs: the nocebo effect [44–47].

Biological treatment is currently part of the medical practice in inflammatory bowel disease management. However, as already discussed in this chapter, the higher cost of the treatment of immune-mediated diseases is directly related to the cost of biological drugs. In this scenario, biosimilar drugs were created. No long ago, higher-than-expected discontinuation of treatment rates possible related to nocebo effect has been observed in patients who switched from a stable treatment with the originator infliximab to the biosimilar CT-P13 [20].

Nocebo effect is a physiological, psychological and neurobiological phenomenon related to a perceived harm that occurs as a consequence of patients' negative expectancies not associated with known pharmacologic actions of the treatment. More recently,

after the beginning of the biosimilar era, the concept of nocebo was revisited and defined as the negative equivalent of the placebo effect. Since then, this concept has received considerable attention in both clinical research and clinical practice [44–46]. Even though medical evidence supports biosimilar use, several barriers were created to hinder more widespread adoption of these drugs into current medical practice. Slow uptake of biosimilars in clinical practice may reflect gaps in patients' and clinicians' knowledge and understanding of these drugs risks and benefits. For sure, this fact has stimulated interest in the potential role of nocebo phenomenon [20, 47, 48].

It has been proposed that different neurobiological pathways may play a role in the effect of negative expectations on patients' perceptions. In fact, the majority of the studies came from the field of pain perception, a method to better understand nocebo effect. Some pathways were supposed to be involved: activation of the hypothalamic-pituitary-adrenal axis and CCKergic systems (CCK = cholecystokinin), as well as decreasing dopamine and opioid activity may play a role in the pathophysiology of nocebo effect. The neuroanatomical regions contributing to the nocebo effect are most likely different than those contributing to the placebo effect [48].

Odinot and colleagues analyzed the nocebo effect in a systematic review. Authors concluded that there are insufficient data published to confirm a biosimilar nocebo effect, although higher discontinuation rates in infliximab biosimilar open-label studies support this theory. They also outlined many limitations in this systematic review to draw strong conclusions. Further studies are needed to evaluate the existence of a biosimilar nocebo effect. If it does indeed exist, the effects of mitigation strategies such as prescriber education and patient empowerment should be evaluated [47].

The nocebo effect, at least in part, may be responsible for higher rates of discontinuation of treatment after switching from an innovator biological to a biosimilar. In the aforementioned systematic review and meta-analysis by Queiroz et al., our group reported that discontinuation rates following a switch to a biosimilar in patients with IBD increase over time. However, it was not possible to confirm the nocebo effect as the unique reason for discontinuation [20].

6. Biosimilar knowledge among IBD specialists

In the earliest years of marketing of biosimilars, the perspective of IBD specialists regarding biosimilars was very conservative [49]. Previous survey-based studies with gastroenterologists have shown a significant unawareness of biosimilar medications in general [50, 51]. On the other hand, it has been previously demonstrated that educational initiatives can increase confidence regarding biosimilar use in clinical practice [52]. Little is known about the comprehension and perception of Brazilian gastroenterologists about biosimilars. In 2016, the Brazilian Study Group of Inflammatory Bowel Diseases (GEDIIB) conducted an anonymous web-based survey with IBD-expert gastroenterologists regarding their current knowledge of biosimilar monoclonal antibodies. The volunteers responded to 22 multiple-choice questions contemplating issues such as their confidence and concerns of using biosimilars, their opinion about non-medical switching and their need of educational activities. To evaluate changes in perception of specialists, a similar follow-up questionnaire with 14 multiple-choice questions was later developed by the GEDIIB. It was delivered during the II Brazilian Congress of Inflammatory Bowel Diseases audience, between March 29 and 31, 2019. Both surveys were non-interventional and offered self-selective recruitment. A simple descriptive comparison of data between the two questionnaires was carried out.

6.1 2016 survey demographics

A total of 61 respondents replied to the survey. Most worked in private clinics (72%) and in public hospitals (49%), and 70% occupied high positions, such as professors, head of Gastroenterology departments and head of IBD units. The majority of them lived in the southeastern region, where the most developed IBD referral centers are located in Brazil. In total, 95% answered that they were responsible for biologic therapy prescription and two-thirds of them had more than 5 years of experience in prescribing biologics.

6.2 2019 survey demographics

The similar questionnaire was applied to 731 gastroenterology physicians. Most of the volunteers responded that they lived in the southeastern region, 41% worked in public hospitals, while 39% worked in private clinics. The majority of the physicians (67%) declared to have access to biosimilars; however, 40% had never prescribed the medication.

6.3 Comparing the survey results

The majority of participants considered that biosimilars are less expensive (77% in 2016; 86% in 2019) than the originator. In both surveys, about half of the responders thought that biosimilars have equivalent efficacy, and about 14% thought that biosimilars will have more indications than the originator. In 2019, a much lower percentage of participants considered that the immunogenicity of biosimilars is the same than the originator (21% compared to 47% in 2016). **Figure 2** summarizes the answers to general concepts of biosimilars.

The majority of responders disagreed with substitution of the originator with a biosimilar by a pharmacist (82% in 2016; 92% in 2019), although, in 2019, 8% agreed with automatic substitution only for new prescriptions. When asked if they would switch a patient in remission from the originator to a biosimilar, most (92% in 2019) responded they would not make a switch, even in patients with sustained remission. **Figure 3** illustrates the responses regarding substitution and switch.

Expert gastroenterologists still show concerns regarding the efficacy and safety when prescribing biosimilars. The percentage of totally confident and very confident to prescribe these medications decreased from 23% in 2016 to only 4% in 2019, while 56% of respondents were little confident and 21% have no confidence in prescribing this medication in 2019—worse compared to 2016. **Figure 4** summarizes confidence in biosimilars.

In the 2019 survey, 59% of participants reported that education in biosimilars is confusing and the majority agreed that educational activities involving biosimilars are needed (94%), as well as greater collaboration between societies to develop guidelines in biosimilars (95%) and the development of records for monitoring the safety of biosimilars (99%).

In a recent similar survey, European IBD physicians were asked about the use of biosimilars in 2013 and 2015. Unlike our research, their study demonstrated that a better understanding of the process of developing biosimilars and their regulatory process contributed to a change in the perception of IBD experts about biosimilars and, consequently, they became more confident in prescribing biosimilars [52]. Conversely, in our study, there was a worsening in the confidence of IBD physicians in prescribing biosimilars over time. This difference between the European and Brazilian surveys may reflect the lack of knowledge of Brazilian physicians about biosimilars and shed light for the development of appropriate educational strategies in Brazil.

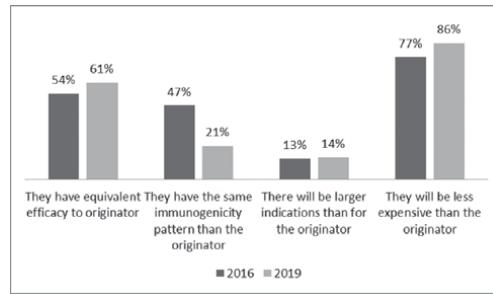


Figure 2.
General concepts of biosimilars in 2016 and 2019.

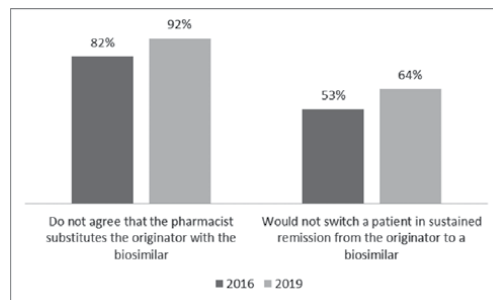


Figure 3.
Responses regarding substitution and switch in 2016 and 2019.

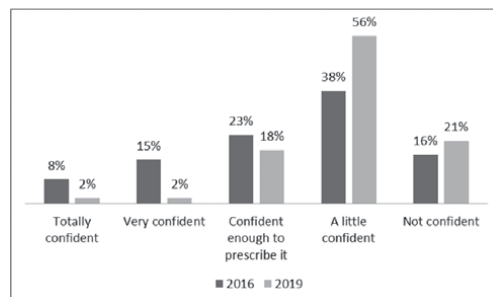


Figure 4.
Confidence in biosimilars in 2016 and 2019.

7. Conclusions

As the patents of biologics are expiring, biosimilars represent a promising opportunity to expand access to biological therapies due to price competition and cost savings. Although this chapter provides a comprehensive overview of the current state of knowledge on biosimilars in IBD, knowledge gaps remain, especially concerning different strategies of switching (e.g., cross-, multiple-). The widespread adoption of biosimilars will enable increasing knowledge and experience with biosimilars, which will pave the way toward an improved acceptance and decreased negative expectations with the incorporation of these drugs in clinical practice.

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Rheumatic Diseases and Biosimilars: Evidence about Switch from Originators to Biosimilars in the Real Life

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Abstract

Biosimilars are broadly available for the treatment of several diseases including inflammatory arthritis. Thanks to biosimilars it has been possible to treat a greater number of rheumatic patients who previously were undertreated due to the high cost of originators, in several countries. There are a lot of data from double blind, randomized, controlled clinical trials, especially on TNF inhibitors (TNFi), concerning the maintenance of clinical efficacy after switching from originators to biosimilars; therefore, such a transition is increasingly encouraged both in the US and Europe mainly for economic reasons. However, despite the considerable saving, such shifts to biosimilar drugs are still being debated, principally over their ethical implications. Since the drugs are similar but not identical, the main issues are related to the possibility to compare the adverse events and/or the lack of efficacy and, to date, the variability in effectiveness for a single patient remains an unpredictable datum before effecting the switch. Despite encouraging data about the maintenance of efficacy and safety after the switch, there are many reports of discontinuation due both lack of efficacy or and adverse events. In this chapter we aim at showing the disease activity trend and the safety after the transition to TNF-i biosimilars in patients with rheumatic diseases in real life..

Keywords: Infliximab, Etanercept, Adalimumab, real-life, originator, biosimilar, switch

1. Introduction

As previously stated, a biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference product (RF). Before they are approved, biosimilars are requested to undergo a precise development process in order to establish biosimilarity when compared to their originator. The European Medicines Agency's (EMA) Scientific Committees evaluate biosimilars according to the same standards that apply to all biological medicines; in fact, every new biosimilar is required to produce studies that show to what extent it is similar to the RF originator and that there are no clinically

meaningful differences between them in terms of safety, quality and efficacy. This element allows avoiding the repetition of clinical trials already carried out with the originator in the first place; in fact, rule no. EMA/CHMP/BWP/3354/1999 clearly states that “(...) biologic drugs are required to undergo proper studies for each registration and disease of pertinence” [1]. In order to get the approval, each biosimilar must give a coherent justification as to why the indication in question makes use of extrapolation instead of carrying out a comparative study in each case [2]; in this context, the extrapolation allows the indication of a biosimilar to be transferred to another indication where only the originator was tested without performing additional clinical studies with the biosimilar in the other indication due to their aforementioned similarity which is given by the definition itself. However, there are concerns that these differences may impact on efficacy or safety in certain indications, which extrapolations cannot establish properly.

Nevertheless, given the efforts inferred by the development and the analysis of the studies requested to approve the originators, biosimilars can only be authorized once the period of data exclusivity on the ‘reference’ biological medicine has expired; in general, this timelasts for at least eight years from the marketing authorization [3].

Despite the approval given by the European League Against Rheumatism (EULAR) to insert the possibility to use biosimilars in the guide lines, it is quite manifest that, to date, both a certain struggle and a severe mistrust in the usage of such biosimilars are still very present among clinicians and patients [4]. These problems origin from various concerns; one of the main complications in the usage of biosimilars comes from double-blind randomized controlled trials (RCTs) concerning the maintenance of clinical efficacy after switching from originators. To date, many studies have been showing conflicting results on the topic, which has led physicians to mistrust the clinical effectiveness of the switch for patients in therapy with originators [5]. Contrariwise, more and more studies and societies are gathering data confirming that comparable efficacy and tolerability were observed in patients who switched since data support the long-term efficacy of biosimilars in patients with rheumatic diseases [6]. In fact, in the majority of studies, efficacy endpoints were maintained in the switch group as well as the number of patients with remission as per ACR/EULAR criteria.

One of the most important studies, NOR-SWITCH, was published in 2017 on *Lancet*; its main purposes were to evaluate the switch from originator infliximab (IFX) to biosimilar CT-P13 and to compare its effectiveness with the maintained treatment with IFX. In order to achieve this goal, a 52-week, randomized, double-blind, non-inferiority trial was performed gathering data from 40 Norwegian study centres. Only patients on stable treatment with the originator for at least 6 months before randomization were included. Two hundred and fourty one out of 481 patients were on continued treatment and 240 were switched from the originator to CT-P13. The frequency of adverse events was similar between groups, and switching was not shown to affect clinical endpoints. The results of this study strongly revealed that switching from the originator to the biosimilar TNF-i does not result in worse outcomes than continued therapy with the originator with the assumed non-inferiority margin of 15%. Similar results were obtained from other important studies in patients with Rheumatoid Arthritis such as PLANETRA (71.8% and 71.8%, respectively, for ACR20, 48% and 51.4%, respectively, for ACR50, and 24.3% and 26.1%, respectively, for ACR70) as well as from registries like DANBIO; these two elements predominantly focused on IFX.

Another valuable aspect has to be considered whilst discussing the shift to biosimilars: Health technology assessment (or HTA). The rationale for a biosimilar is to promote competition among manufacturers to lower prices and potentially increase access to affordable therapies.

A Canadian study concerning biosimilars and their impact on health-related budget showed that in a two-year period of time, approximately one billion dollars in savings could have been realized through exclusive purchasing of biosimilar drugs for IFX, filgrastim, and insulin glargine as opposed to the originator products [7]. However, to date, in the US this phenomenon is not as frequent as it appears to be in Europe since a report compiled in 2018 indicated that only 3% of biologic spending (which is equivalent to US\$3.2 billion) is subject to competition from biosimilar products [8].

Nonetheless, despite the considerable saving, such shifts to biosimilar drugs are still being debated, principally over their ethical implications. Since the drugs are similar but not identical, the main issues are related to the possibility to compare the adverse events and/or the lack of efficacy and, to date, the variability in effectiveness for a single patient remains an unpredictable datum before effecting the switch. Despite data about the maintenance of efficacy and safety after the switch, there are many reports of discontinuation in real life data due both lack of efficacy or adverse events.

The European Medicines Agency (EMA) was the first regulatory body to develop a specific regulatory pathway for the approval of biosimilars when it published 'Guidelines on similar biological medicinal products' in 2005 [9]. Since then, many biosimilar agents have been approved by regulatory agencies in Europe and North America. The first biosimilars were the somatropin analogs, introduced in Europe. Erythropoietin biosimilars followed in 2007.

The TNF- α biosimilars approved in Rheumatology are biosimilars of 3 molecules, IFX, ETA and Adalimumab (ADA).

2. Immunogenicity

Immunogenicity is by definition the property of a substance to induce an immune response usually mediated by the adaptive immune system [10]. When applied to the pharmacological field, immunogenicity may represent both a desired (e.g., with the use of vaccines) or undesired (e.g., during a treatment with biological agents) event. Big molecules, like monoclonal antibodies (moAbs) or their derivatives are high inducers of immunogenicity. Besides the size, many other factors can influence drugs' immunogenicity, including variables related to the recipient (demographic characteristics, genetics, underlying disease, concomitant immunosuppressive drugs) or to the drug itself (impurities, posttranslational modifications, doses, route and intervals between two consecutive administrations) [11]. In modern times, manufacturing techniques for the production of moAbs have evolved in order to restrain the degree of unwanted immunogenicity. One example is the process of humanization of moAbs, aiming at the replacement of primitive mouse domains with human ones [12].

The class of TNF- α agents used for rheumatic diseases includes antibodies with different molecular structures. Three of them (IFX, ADA and golimumab) are full-length moAbs belonging to the human isotype class IgG1. IFX is a chimerical antibody, retaining 25% of the original murine structure, while ADA and golimumab are fully human moAbs. Etanercept (ETA) is a fusion protein consisting of two identical tumor necrosis factor receptor-2 (TNFR2) regions linked to the fragment crystallizable (Fc) of a human IgG1. Finally, certolizumab-pegol is a monovalent Fab fragment of a humanized anti-TNF α antibody conjugated to two molecules of polyethylene glycol (PEG) [13]. Though each of them works by neutralizing the pro-inflammatory cytokine TNF- α , differences in their molecular structures likely account for separate mechanisms of action and immunogenicity rates. Chimerical and human full-length moAbs are able to bind either soluble or transmembrane

TNF- α in a more efficient way than other TNF-i, eliciting complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and reverse signaling effects, including apoptosis, in transmembran TNF α -bearing cells [14]. In addition, TNF-i agents having the Fc can mediate other biological effects in Fc γ R-bearing cells like monocyte-macrophages, which may result either in the potentiation of immunetolerance or in the release of pro-inflammatory cytokines. This dual effect likely depends on the interaction of the drugs with different types of FcR, which may intracellularly transduce an inhibitory or activating signal.

This premise on the molecular characteristics and mechanisms of action of the licensed TNF-i is essential for clarifying many aspects related to the immunogenicity of these drugs. Immunogenicity rates, in terms of anti-drug antibody (ADAb) formation, are in fact highly variable among patients undergoing TNF-i therapy [15]. Studies reported higher ADAb titers in rheumatoid arthritis (RA) patients treated with ADA and IFX and lower ADAb titers in patients treated with ETA, certolizumab pegol and golimumab [16]. The production of ADABs in IFX-treated patients may be attributed to the chimerical structure of the drug. Similarly, ADABs synthesized in ADA-treated individuals may recognize murine epitopes located in the complementarity-determining regions of ADA combinatory sites [17]. Moreover, full-length moAbs, like IFX and ADA, may be captured by dendritic cells by means of a Fc-dependent phagocytosis and antigenic fragments of the drugs may be presented to T helper (Th)₂ lymphocytes, with the following stimulation of a humoral immune response leading to ADAb production [12]. The latter mechanism could be particularly pronounced in rheumatic patients having a constitutional hyper-activation of the B cell compartment, like those suffering from RA.

Serum ADABs can be measured by means of several assays that display some sensitivity and specificity limits. They include the enzyme-linked immunosorbent assay (ELISA) and the electrochemiluminescence (ECL) assay, both based on bridging formats, the radioimmunoassay (RIA) and other antigen-binding tests (ABT) [15]. ELISA and ECL may underestimate the presence of monovalent ADAs, like those having an IgG4 isotype, while ABT seem to have higher sensitivity.

ADAb titers can widely vary according to sampling time and antibodies may belong to distinct isotype classes, have different affinity for the ligand or a variable degree of ligand neutralization [15]. ADAb belonging to the IgM, IgG, IgA and IgE isotypes have been reported in patients undergoing TNFi treatments [18, 19]. These antibodies can already be detected in the serum of IFX-treated patients between the second and the third infusion, whereas they may appear after 6 months of treatment in patients assuming ETA or ADA. Crucial is also the identification of neutralizing and non-neutralizing antibodies. The first may have a noteworthy impact on the efficacy of TNF-i treatment, whilst the second can play a major role in immunogenicity and immunogenicity-related adverse events, such as anaphylaxis, infusion reactions or cross-reactivity phenomena to endogenous proteins [11].

Recently, the introduction of drug-tolerant assays has allowed the possibility to detect immunocomplexes of ADABs bound to TNF-i drugs, providing very relevant information in selected cases. The formation of immunocomplexes may in fact be at basis, on the one hand, of the development of a therapeutic non-response due to a higher clearance of opsonized drug by the reticuloendothelial system, while, on the other hand, it may explain the occurrence of some safety issues, like serum sickness-like reactions [20].

Post-translational modifications can have an additional impact on the biological effects of MoAbs and further influence their immunogenicity. For instance, a reduction in the content of fucose and an increase in the content of galactose and sialic acid of moAbs have shown to potentiate ADCC and CDC, indirectly favoring the clearance of the drug and its phagocytosis by antigen presenting cells (APC) [21].

Finally, immunogenicity may occur as the hyper-activation of immunological axes other than the humoral branch. Our previous studies showed that RA patients experiencing a reduced efficacy or adverse events during the treatment with IFX may have an aberrant expansion of Th1, Th17 and Th9 lymphocytes to the detriment of T regulatory subsets following the *in vitro* exposure to the drug [22, 23]. However, other authors showed that IFX may also favor the differentiation of IL-10-producing T cells having an immunoregulatory phenotype [24].

Immunogenicity is a matter of crucial importance when it comes to biosimilars. Biosimilars may in fact differ from originators in terms of structural characterization, glycan profile and purity/impurity content, which may altogether contribute to slight changes in the mechanism of action (neutralization of transmembrane of soluble TNF α , CDC or ADCC) compared to the originator counterparts [25, 26]. Despite the homology in the primary amino acid sequence, biosimilars may display substantial differences in the secondary (α -helices and β -strands), ternary (disulfide bonds) and quaternary (subunit arrangement and folding) structure as well as in post-translational modifications (glycosylation, oxidation, deamidation, methylation, acetylation, truncated isoforms) [25]. Intentional or unintentional changes to the original molecular structure may take place as a consequence of different manufacturing techniques, cell lines, culture media, purification, ultrafiltration or diafiltration processes.

Several divergences from reference products (RF) have been reported among the class of TNF-i biosimilars. The biosimilar IFX CT-P13 was shown to differ from its originator in terms of charged isoforms and carbohydrate chains, in turn associated with slight differences in the content rate of C-terminal lysine [27, 28]. Furthermore, it was reported an increased amount of fucosylated glycans in CT-P13 compared to the RF [29]. Fucosylation seems to predominantly occur in the Fc domain of CT-P13 and to significantly impair the binding of Fc γ IIIa receptors on monocyte-macrophage cells, thus influencing ADCC and, possibly, immunogenicity by preventing the internalization of the drug into APC [30, 23].

Similarly, the biosimilar ETA SB84 also showed slight differences in the amount of acidic variants, afucosylated and neutral galactosylated glycan content and O-glycan occupancy compared to the RF, despite no effects on its biological activity were reported *in vitro*. Interestingly, a lower particle concentration, aggregate content and product-related impurities were observed in SB4, which may account for reduced immunogenicity rates [31]. In another comparative exercise study, the *in vitro* characterization of the ETA biosimilar GP2015 did not evidence any significant differences with the originator according to the binding affinities to TNF- α , C1q and FcR [32]. When compared to its originator, the ADA biosimilar SB5 was reported to have a slightly higher content in free sulfhydryl groups and acidic variants that were however judged not clinically meaningful. The latter feature likely depends on lysine C-terminus content and degree of sialylation, although they were not associated with changes in SB5 biological activities [33]. Another study aiming to assess the physico-chemical properties of the ADA biosimilar HLX03 reported a slightly lower percentage of high mannosylated glycans in the biosimilar drug, although this did not result in impaired Fc γ RIII binding and ADCC in human peripheral blood mononuclear cells [34].

In line with these preclinical considerations, results from clinical trials or registry data collection reported similar immunogenicity rates with the use of biosimilar and branded TNF-i so that current guidelines and regulatory agencies recommend the use of biosimilars as an effective and safe alternative to originators [5].

The immunogenicity rates between branded and biosimilar IFX emerged from the two randomized controlled trials (RCTs) PLANETRA and PLANETAS enrolling RA and ankylosing spondylitis (AS) patients and from the NOR-SWITCH and

DANBIO registries collecting the data of 482 patients with inflammatory bowel diseases (IBD), psoriasis (PsO) and psoriatic arthritis (PsA) and 802 patients with RA, spondyloarthritis (SpA) and PsA, respectively, appear similar [35]. Patients who were switched from originator to biosimilar IFX did not experience variations in ADAb serum concentration compared to patients who were not switched.

Similar results were obtained with ADA biosimilars. Pharmacokinetics studies conducted on healthy volunteers showed that the production of ADABs, measured through ECL, may occur in up to 70% subjects following a single injection of ADA, being associated with a high proportion of neutralizing antibodies [36]. Although higher ADAb activity was associated with lower serum concentrations of ADA, the proportion of patients developing ADABs was similar among biosimilar and originator treatment arms and ADABs appeared cross-reacting. These data are in line with those of an ex-vivo study analyzing the sera of RA and IBD patients, which showed the presence of shared immune-dominant epitopes between biosimilar and branded ADA [37]. Taken together, these results may also explain the lack of meaningful differences in ADAb titers in patients switched from originator to biosimilar ADA [38]. Phase III RCTs on the use of biosimilar ADA in patients with autoimmune diseases indicate similar or lower percentages of total and neutralizing ADABs, being consistent between the experimental and the traditional arm of treatment. ADAb production has been however associated with a faster elimination of ADA and lower changes in disease activity scores from baseline [39–41].

RCTs conducted on RA and PsO patients treated with ETA biosimilar have shown a reduced percentage of ADAb production in the experimental arm with no detection of neutralizing antibodies [42, 43]. Following the switch from reference ETA to its biosimilar no immunogenicity issue was observed in another RCT on RA patients after 24 weeks [44].

Based on these data and in consideration of the pharmacoeconomic advantages derived from the use of biosimilar rather than branded drugs, it would be natural to incentive the use of biosimilars not only as the first prescription but also as part of a switching strategy. Reassuring efficacy and safety data have in fact emerged from RCTs [39–47], which also reported non-significant variations in ADAb titers following the switch.

Nevertheless, lack of efficacy and reduced retention rates have been observed among rheumatic patients switched from originator to biosimilar TNF- α drugs in real-life. Data from registries on ETA- and IFX-treated RA, PsA and axial SpA patients followed-up for up to one year indicate a lower retention rate in switcher patients compared to historic cohorts, which seems mostly dependent on patients' characteristics, including the underlying rheumatic disease and the disease activity at the time of the switch [48–50]. Since immunogenicity studies are usually not carried out as a part of clinical and laboratory routine, it is unfair whether these results might mirror a real immunogenicity issue or rather represent a nocebo effect [51].

3. Biosimilars in real life

3.1 Etanercept

ETA is a fully soluble human dimeric fusion protein, which competes with soluble human TNF- α for binding cell-surface TNF receptors, precluding the activation of the inflammatory cascade. It is the only fusion receptor TNF- α available, as it differs from other biologics directed against TNF- α which are monoclonal antibodies. This difference may explain its minimal to none efficacy in granulomatous diseases, including inflammatory bowel diseases, uveitis, and ANCA-related

vasculitis; on the other hand, ETA showed a better retention rate and a lower impact on the reactivation risk of tuberculosis infection [52].

ETA was the first TNFi approved in the United States (US) and Europe.

In 1998 and in 2000 respectively, ETA was approved by FDA (Food and Drug Administration) and EMA for the treatment of RA; shortly after this authorization, new indications were approved, including polyarticular juvenile idiopathic arthritis (JIA), PsA, AS, PsO and pediatric-PsO.

To date, three biosimilars of the originator ETA (Enbrel®) are available. On January 2016, SB4 (known as Benepali® in Europe) received the authorization from EMA for the same indications of its originator, whilst FDA approved its use in the US on April 2019 (Eticovo®). GP2015 (Erelzi®) was approved by EMA on June 2017 while YLB113- (Nepexto®) on May 2020. All of these biologics have demonstrated the bioequivalence with the RF in clinical trials [42, 53–56] for at least one of the approved indications given to the originator and, based on the same mechanism of action, indications have been extrapolated for all approved indications (**Table 1**) [57]. Other biosimilars of ETA, approved neither by EMA nor by FDA, are available in the rest of the world [58].

Due to disputes about these extrapolations and the unrequested need to confirm the safety and efficacy of biosimilars in real life in rheumatic diseases, numerous real-life studies have been published in the last years. The vast majority of real-life data are focused on SB4, while more data derive from registries. One of the first established registries to compare SB4 with reference ETA was the nationwide observational Denmark DANBIO registry that included patients treated with ETA originator (2061) switched to SB4 (1621–79%) affected by RA, AxSpA and PsA (77%, 77% and 86%, respectively). The switched patients had a low disease activity and stable disease during the 3 months before the switch and received DMARDs less frequently than non-switchers. After one year of observation, authors found a lower retention-rate in SB4 population compared with the retention rate of a historic ETA originator cohort. They also found a higher withdrawal rate among non-switchers - 32.9% (145/440) - vs. switchers 18.4% (299/1621); however, disease activity was found to be higher in this group. During the follow-up, among the 299 withdrew switchers to SB4, 120 patients needed to be switched back to the originator due to lack of efficacy. A sub-analysis of this group showed that the main reason SB4 failed was attributable to the patient perception of the disease (PGS - patient global score) rather than CRP or tender/swollen joints. The authors concluded that reasons to withdraw treatment were more frequently related with patients'

Indications	IFX	ETA	ADA
Rheumatoid Arthritis	√	√	√
Juvenile idiopathic arthritis	—	√	√
Psoriatic arthritis	√	√	√
Ankylosing Spondylitis	√	√	√
Crohn's disease	√	—	√
Ulcerative colitis	√	—	√
Plaque psoriasis	√	√	√
Pediatric Crohn's disease	√	—	—
Pediatric ulcerative colitis	√	—	—

Table 1.
TNF-inhibitors approved indications.

factors, such as being in remission or not and with subjective perception rather than objective evidence of poor disease activity control. No major adverse events were observed after the switch [48].

To date, data on SB4 from spontaneous studies are available.

A review published in 2019 focused on real world evidence about SB4, identifying 13,552 patients that used this biosimilar in Europe; among these patients, 11,053 switched from the reference ETA while 768 (6.9%) switched back to the originator. The majority of patients included were affected by RA, PsA and SpA; there were also a small percentage of psoriatic patients without arthritis (2.5%) and a negligible proportion of patient affected by other inflammatory related diseases (Juvenile Arthritis and IBD, 0.1%). Outcomes included the effectiveness of SB4 evaluated with a comparison between pre-switch and post-switch disease activity, retention rates, reasons for discontinuations, the evaluation of back-switchers, acceptance of the switch. In general, the results of this extensive review confirmed the efficacy of SB4 without statistically significant changes in laboratory or clinical parameters of inflammation and disease activity. No meaningful differences in the number of adverse events were observed before and after the switch, confirming its safety. However, a proportion of patients ranging between 3 to and 7.5 % switched back to the RF. Data about small studies showed that disease flares documented by ultrasound, CRP values or clinical examination represent the main reasons to switch. On the other hand, data about from DANBIO registry highlight the subjective factors (such as tender but not swollen joint count with, no differences in CRP serum levels) as the main reason to be switched back to the RF. The percentage of switching back was comparable to the smaller studies (7%). Retention rates of the included studies were at least 75% at 12 months of follow-up. By comparing results of two large registries (Spanish BIO-SPAN [59] and Danish DANBIO [48]) authors found that the obligatory nature of the switch was not necessarily related with a higher acceptance rate; Spanish, Danish and Swedish [60] registries shared a higher concomitant use of methotrexate in the switchers. Other variables, such as the duration of usage of the originator and disease activity at the time of the switch were variably related with the degree of acceptance. A proper communication with the patient seemed to improve the acceptance rate of the switch as some authors found out that the older the patient or the longer the disease duration, the less accepted was the switch. Globally, acceptance rates ranged between 51.6% and 99.0%. The RABBIT registry confirmed the data of the registration study reporting lower rates of site reaction in patients treated with SB4 vs. the originator [61]. Differences in treatment practices, lack of clinician confidence with the drug and nocebo effects could have influenced this report [62].

More recently, two independent Italian groups published results from their SB4 switch cohort from originator.

Both studies included patients affected by RA, PsA and AxSpA, treated with ETA originator who switched to ETA SB4.

The former is a single center study including 80 patients in low disease activity. The aim was to evaluate the disease activity trend after the switch, comparing the trend during the 12 months before the switch with the trend at 12 months after switch through the analysis of disease activity parameters currently used for each diagnosis. Data analysis did not show significant differences in any of evaluated parameters after the switch from originator to biosimilar. A percentage of 12.6% (11 out of 85 patients) interrupted the treatment with the biosimilar due to lack of efficacy (7/11) or subjective features (2/11) or adverse events (2/11) which have been classified as not serious [63]. No correlation with demographic data, concomitant therapy or disease duration was found.

The second study included 220 patients in stable clinical conditions, from 2 Italian University Hospital, in treatment with originator for at least 6 months; the period of observation was at least 6 months. Among them, 165 patients were observed up to 12 months while 65 patients were observed up to 18 months. Treatment persistence was observed to be 99.1%, 88.6% and 64.6% at 6, 12 and 18 months, respectively. The interruption was due to lack of efficacy in the majority of cases (19 patients), while it was discontinued due to safety issues in 11 patients. No interactions with other demographic or disease factors were found in this study as well [64].

In the overall data available about back-switching, the main reason was lack of efficacy, strictly followed by adverse events. However, the former was reported to be subjective by many authors.

3.2 Infliximab

IFX is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by using recombinant DNA technology; it is approved for RA, AS, PsA, Crohn Disease (CD), Crohn Disease (CD), Ulcerative Colitis (UC) and PsO [65].

The originator product, Johnson & Johnson and Merck's Remicade (IFX), was approved by the FDA in August 1998 and by the EMA in August 1999 [66].

The patents of reference IFX expired in the US in September 2018 and in Europe in February 2015. Some of the IFX biosimilars are presented in **Table 2**.

The NOR-SWITCH extension trial aimed to assess efficacy, safety and immunogenicity in patients who used IFX CT-P13 throughout the 78-week study period (maintenance group) versus patients who switched to IFX CT-P13 at week 52 (switch group).

Three hundred and eighty patients were recruited (197 in the maintenance group with the RF and 183 in the switch group). In the full analysis set, 127 (33%) had CD, 80 (21%) UC, 67 (18%) SpA, 55 (15%) RA, 20 (5%) PsA and 31 (8%) PsO. The primary outcome was disease worsening during follow-up based on disease-specific evaluation parameters. The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 and patients who switched from originator IFX to CT-P13, supporting the assertion that switching from originator IFX to CT-P13 is both safe and effective [69].

Other interesting data come from a French study published in 2018 by Avouac and coworkers [70], in which no change in objective disease activity measures nor in IFX levels were observed in 260 patients with chronic inflammatory diseases who were receiving maintenance therapy with innovator IFX and systematically shifted to biosimilar IFX CT-P13; 31 of them (11.9%) had RA and 131 (50.4%) had axSpA while the others had other inflammatory diseases (IBD above all). The retention rate was observed to be 85% (221 out of 260 patients) at the time of the third biosimilar infusion. From the beginning of the switch to the last visit (mean follow-up of 34 weeks), 59 patients (23%) discontinued biosimilar IFX, mainly due to lack of efficacy (47, 80%). However, no clinical or biological factors were associated with biosimilar discontinuation. No serious adverse events occurred. No change in disease activity parameters or IFX levels was detected. However, a significant increase of BASDAI (2.94 ± 2.20 vs. 3.18 ± 2.21 , $P = 0.046$, before vs. after switch, respectively) was observed in patients with axSpA. Sensitivity analyses for effectiveness included changes of disease activity parameters and IFX levels between baseline and the last visit as well as the occurrence of adverse events leading to drug discontinuation. No changes in IFX levels or objective parameters were observed after the systematic switch to biosimilar IFX in a real clinical practice setting.

Company name	Product name	Stage of development
Amgen, USA	Avsola (ABP 710)	Approved by FDA in December 2019
Biocad, Russia	BCD-055	Non-originator biological approved in Russia in Feb 2018
Celltrion/Hospira (Pfizer), South Korea/USA	Remsima/Inflectra (CT-P13)	Intravenous version approved in EU in September 2013. Subcutaneous version approved in September 2019. Approved by FDA in April 2016.
	Ixifi (PF-06438179)	Pfizer received FDA approval for Ixifi in December 2017.
Epirus Biopharmaceuticals, USA	Infimab	'Similar biologic' approved in India in September 2014
MabTech/Sorrento Therapeutics, China*/USA	STI-002	Positive phase III trial for copy biological in China reported in January 2016
Mabpharm/Sorrento Therapeutics, China*/USA	CMAB008	Copy biological submitted to China's NMPA for approval in January 2020
Nichi-Iko Pharmaceutical, Japan	NI-071	Phase III trial in rheumatoid arthritis expected to be completed in March 2015. Approved in Japan in September 2017. US phase III trial in rheumatoid arthritis expected to be completed February 2019.
Nippon Kayaku, Japan	IFX BS	Approved in Japan in November 2014
Ranbaxy Laboratories/Epirus Biopharmaceuticals, India*/USA	BOW015	'Similar biologic' approved in India in December 2014. Global phase III trial expected to be completed in July 2017.
Samsung Bioepis (Biogen/Samsung/Merck), South Korea/USA	Flixabi (EU)/Renflexis (US) (SB2)	Approved in EU in May 2016. Approved by FDA in April 2017.
Sandoz, Switzerland	Zessly (PF-06438179)	Sandoz acquired EEA rights from Pfizer in February 2016. Approved in May 2018
Shanghai Biomabs Pharmaceuticals, China	Baimaibo	Phase III trial in RA in China started March 2018

EC: European Commission; EEA: European Economic Area, this area includes the 28 EU Member States, plus Iceland, Liechtenstein and Norway; EMA: European Medicines Agency; EU: European Union; FDA: US Food and Drug Administration; NMPA: National Medical Products Administration. Adapted by <https://www.gabionline.net/Biosimilars/General/Biosimilars-of-IFX> [67, 68].

Table 2.
Biosimilars and non-originator biologicals of IFX.

Patient-reported outcomes were the only to be observed; a possible explanation could be, again, the nocebo effect rather than proper pharmacological differences, as demonstrated by the stability of objective measures (i.e. swollen joint count), CRP values and plasma levels of the drug.

Data from registries including DANBIO [49], also support the safety and efficacy of changing from a bio-originator to its biosimilar. The DANBIO registry evaluated 802 patients affected by RA, PsA and axial spondyloarthritis (AxSpA) who switched from originator IFX (IFX, Remicade) to biosimilar IFX CT-P13. The average follow-up was 413 (339–442) days. Disease activities 3 months before and after the switch as well as the changes over time were calculated. 1-year CT-P13 retention rate was similar to the historic IFX cohort (84.1 vs. 86.2) and did not differ

significantly from the bio-originator. Results showed that 132 patients discontinued biosimilar IFX due to lack of effect (71/132 = 54%), followed by adverse events (37/132 = 28%). Authors found that patients with previous IFX treatment with a duration of >5 years had longer CT-P13 retention.

Smaller 'real-world' observational studies also confirmed comparable efficacy and safety of transitioning from originator to biosimilar IFX CT-P13 to that of continuing treatment with biooriginator IFX [71, 72].

In a single centre in Finland, Nikiphorou and colleagues observed similar patient-reported disease activity and symptoms after transitioning to biosimilar IFX CT-P13. Thirty-nine consecutive patients with RA (38%), AS (36%), PsA (18%), juvenile idiopathic arthritis (JIA) (5%), chronic reactive arthritis (3%), were switched to biosimilar after a mean (SD) of 4.1 (2.3) years on IFX. Thirty-one patients were on concomitant methotrexate.

At a median (range) of 11 (7.5–13) months following the first administration of IFX-biosimilar-CT-P13, disease activity and patient reported outcomes (PROs) were similar for IFX-originator and IFX-biosimilar-CT-P13. Eleven patients (28.2%) discontinued biosimilar-CT-P13, due to anti-IFX originator antibodies (n = 3), subjective reasons with no objective deterioration of disease (n = 6) or other causes (latent tuberculosis, n = 1, new-onset neurofibromatosis, n = 1); the clinical effectiveness of IFX biosimilar in both PROs and disease-activity measures was comparable to IFX originator during the first year of switching. Authors did postulate that subjective reasons (negative expectations) may play a role among discontinuations of biosimilars [73].

Similar results were obtained by German and colleagues [74], that aimed to assess the long-term retention rate of CT-P13 after switching from originator IFX, which appeared to be identical to a historical cohort, confirming the safety, efficacy and acceptability of the switch in the long term (median follow-up of 120 weeks; range 6–145). Among the 39 withdrawals, 25 (64%) patients discontinued CT-P13 during the first period of follow-up. Reasons for stopping CTP-13 belatedly included an objective clinical worsening in 5/14 patients, non-serious safety issues in 6/14 patients (psoriatic lesions, digestive disorders, asthenia and subjective neurological symptoms with negative extensive investigations and stable remission in 3/14 patients). No case of subjective clinical worsening was observed during the second period of the follow-up. The weight of patients' acceptance was also taken into account in a cohort of 89 patients (63 AS, 12 PsA and 14 RA) that agreed to switch from the originator to CTP-13 [75]. After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. This rate of maintenance was significantly lower than the one found in the historical control cohorts and prospective study cohorts: 88% and 90% respectively (p = 0.0002). Among patients requesting a return to the originator, 13/25 (52%) showed clinical activity for their disease, one patient presented with serum sickness and 11 (44%) did not exhibit objective activity. An analysis excluding these 11 patients eliminated the difference in retention rate between the 3 cohorts (p = 0.453) suggesting patient reluctance to switch and negative perception of the biosimilar.

After returning to the originator, patients without objective clinical activity all returned to their previous state.

In a cohort of 222 patients treated with originator, 192 agreed to switch to CT-P13 as they were included in a Dutch multicenter prospective cohort study (BIO-SWITCH) [76]. Patients with a clinical diagnosis of either RA, PsA, or AS who agreed (transition group) or did not agree (control group) to transition to CT-P13 were both eligible for inclusion in the study. During 6 months follow-up, 24% of the patients (n = 47) discontinued CT-P13. 37 patients restarted originator, 7 switched to another biologic drug, and 3 continued without a biologic drug.

The DAS28-CRP remained stable from baseline to month 6. The BASDAI slightly increased (difference of +0.5 [95% CI 0.1, 0.9]); CRP, IFX levels and anti-IFX antibody levels did not change. Just before CT-P13 discontinuation, DAS28-CRP components tender joint count and patient's global assessment of disease activity, as well as BASDAI, were increased when compared to baseline. The most frequently reported AEs were arthralgia, fatigue, pruritus, and myalgia. One-fourth of patients discontinued CT-P13 during 6 months of follow-up, mainly due to an increase in the subjective features of the tender joints count and the patient's global assessment of disease activity and/or subjective symptoms, possibly explained by placebo effects and/or incorrect causal attribution effects.

Boone and colleagues [77], aimed to investigate the role of the placebo effect in a cohort of 125 patients enrolled in the study (73 CD, 28 UC, 9 RA, 10 PsA and 5 AS). As expected they have shown no statistically significant changes in effectiveness and safety in any of the indications after a median of 4 infusions in 9 months but they highlighted the placebo response of 12.8% was found among the patients during a minimal observation period of 6 months after the transition to biosimilar IFX without differences between the indications.

For SB2 the real-life data available are fewer and they are related to Inflammatory Bowel diseases and PSO [78]. In the work of Fautrel [78], only Four SAEs were reported: one considered related to SB2 (infected cyst) and three unrelated (two RA disease flares and one overdose of vitamin K antagonists).

There is less evidence regarding the cross-switch from different IFX biosimilars.

Gisoni et al. [79] investigated the effectiveness and safety of cross-switching from CT-P13 to SB2 in 24 patients with PsO and they concluded that it was not associated with a significant change in PASI score or additional adverse events.

Same result were obtained by Bazzani et al. [80]. The Authors retrospectively evaluated the efficacy and safety of the sequential use of 2 biosimilars of IFX in 50 patients already being treated with Remicade® for AS (25 patients), RA (15 patients) and PSA (10 patients) and they did not find significant alterations in the clinical response. The safety profile was also not modified by this therapeutic model.

3.3 Adalimumab

In 2002 Humira, the originator ADA, became the third TNFi to be approved in the USA after IFX and ETA. ADA has shown excellent efficacy and safety and it is widely used in clinical treatment for RA [81]. It is the best-selling drug worldwide, with global sales worth \$18 billion in 2017 alone [82]. It is also one of the most versatile drugs, seeing as it has been approved SpA, PSO, PsA, CD, UC, polyarticular juvenile idiopathic arthritis (JIA), hidradenitis suppurativa (HS) and noninfectious uveitis [83].

Currently, seven ADA biosimilars are approved either in the EU and/or the USA: ABP 501, BI 695501, FKB327, GP2017, MSB11022, PF-06410293 and SB5, all of which have been proven to be similar in terms of safety and efficacy to the licensed RF (RP). ADA is a recombinant, fully human, IgG1 monoclonal antibody that is structurally and functionally indistinguishable from naturally occurring human IgG1. It was engineered through phage display technology and it is produced in a Chinese hamster ovary cell line [84]. ADA is administered by subcutaneous injection and its peak plasma concentration is reached after approximately 131 h. It possesses a widely distribution which includes the synovium. Similar to naturally occurring human IgG, its elimination half-life is roughly 10 to 14 days. ADA specifically binds to TNF-alpha (both soluble and membrane-bound) and blocks the interaction with p55 and p75 cell-surfaced TNF receptors [85]. Despite being a

fully human antibody, up to 30% of RA patients develop ADAb again ADA. ADA can prevent the drug from binding to its target and/or forming immune complexes; such phenomena decrease serum drug levels and increase markers of inflammation in RA patients [86]. Amgen's ABP 501 was the first ADA biosimilar to be approved by FDA in 2016 (Amjevita®) and by EMA in 2017 (as Amgevita/Solymbic®). Boehringer Ingelheim's BI 695501 (Cyltezo®) was approved by the EMA and FDA in 2017. Samsung Bioepis's SB5 (Imraldi®) was approved by the EMA in 2017 and by the FDA in 2019. FKB327 (Hulio®) was approved by the EMA and FDA in 2018 and 2020, respectively while GP2017 (Hyrimoz®/Hefya®/Halimatoz®) was approved by the FDA and EMA in 2018, finally MSB11022 (Hidacio®) was approved by the EMA in 2019. PF-06410293 (Abrilada®, Amsparity®) was approved by the FDA and EMA in 2019 and 2020, respectively.

Unlike biosimilar IFX and ETA [87] there are not many open label extension or pharmacovigilance studies for biosimilar ADA.

Despite a lot of data from registration studies, including single switch, multiple switch and switch-back strategies from RF, proving the safety and efficacy of ADA biosimilars, no data on real life switch from ADA-RF to ADA biosimilars are available.

4. Final considerations

Real-life data confirm both efficacy and safety of biosimilars based on large-scale studies.

In clinical practice, the switch from the RF to a biosimilar must be based on a shared decision between the patient and the prescribing physician. It is worth noticing that if a biosimilar gets the “interchangeability” designation allowed by the FDA, it could be automatically substituted at the pharmacy level without consulting the prescribing physician [88]. This designation can be applied only if the manufacturer is able to provide sufficient evidence that “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product (biosimilar) and the RF is not greater than the risk of using the RF without such alternation or switch.” “To date none of the biosimilars have received such designation. Despite controversies regarding the non-medical switch, biosimilars are becoming substitutes of branded biological agents for their lower cost, for the reassuring data on adverse events and serious adverse events not only from registration studies but from real-life studies. Furthermore, biosimilars have the opportunity to make biologic treatment for rheumatic diseases more widely available.

Regarding immunogenicity there are several possible factors that may confound the results. Firstly, concomitant medications might affect the incidence of ADABs and nAbs. In the phase III trials of all biosimilars, patients used MTX while being treated with biologics, but the combination of MTX therapeutic protein-drug interactions, which can then reduce the incidence of ADABs and improve efficacy [89]. Secondly, most of the trials allowed patients to be treated with <2 biologic therapies prior to the start of the trial, which may have a potential impact on the incidence of ADABs and nAbs. Moreover, the incidence of ADABs and nAbs increased with the duration of treatment [90]. Based on the real-life analysis all of biosimilars showed comparable efficacy, safety, and immunogenicity to the RP. Subtle differences are considered to be present due to methodological bias rather than the properties of biosimilars.

The results of studies about the switch from RP to biosimilars, confirmed in most real-life reports, have shown that switching from RP to a biosimilar does not have a significant impact on efficacy, safety, and immunogenicity. Most of the data

regarding the switch-back or the withdrawal treatment showed that the nocebo effect plays a not negligible role, even if objective disease flares can occur.

To conclude, biosimilars will offer exciting opportunities in improving treatment access and increasing treatment options worldwide in the next years. They have the potential to cause an unprecedented impact on the utilization of biologic medications and will continue to challenge originator biologic therapies.

Similar to TNFi biosimilars already on the market, real-world data and pharmacovigilance studies are critical to developing long-term evidence to provide assurances on efficacy as well as safety. These biosimilars will offer exciting opportunities in improving treatment access and increasing treatment options worldwide.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

A special thanks to Loredano Giorni: his humanity and expertise strengthened our moral values concerning the sustainability of health care systems so that more people can be cured and further resources can be deployed to get innovative drugs.

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Monoclonal Antibodies for Cancer Treatment

Annemeri Livinalli and Taís Freire Galvão

Abstract

Therapeutic monoclonal antibodies have emerged in the 1990 decade as an important option for cancer treatment. These molecules have a diverse set of clinically relevant antitumor mechanisms, directly targeting tumor cells. It has been established as “standard of care” for several human cancers. This chapter reviews the use of monoclonal antibodies in oncology and introduces available biosimilars. The requirements for biosimilar antibody development, mechanisms of action and current clinical applications for cancer treatment is also presented.

Keywords: biosimilar, equivalence trial, efficacy, monoclonal antibodies, cancer, extrapolation of indication

1. Introduction

Since the development of monoclonal antibodies by hybridoma technology in 1975 [1] over 80 molecules were developed and approved for therapeutic use in immunological, oncological, and infectious diseases [2]. Over time, these molecules have revolutionized the treatment of main autoimmune diseases and cancer that previously had a bleak prognosis. These molecules are usually administered by subcutaneous or intramuscular routes due to poor oral bioavailability (less than 1%) caused by large size, polarity, limited membrane permeability, and poor gastrointestinal stability [3].

In oncology, the approach in the use of monoclonal antibodies consists in targeting tumor antigens and killing cancer cells [4]. Growth factor receptors that are overexpressed in tumor cells are recognized as main target by monoclonal antibodies [4, 5]. Blocking ligand binding/signaling result in decrease growth rate of cancer cells, which in turn, induce apoptosis and sensitize tumors cells to chemotherapy [6, 7].

As of the first semester of 2021, the arsenal of monoclonal antibodies in oncology counts on more than 30 molecules [8]. Among the first molecules, we have: bevacizumab, cetuximab, rituximab, trastuzumab, indicated for treating solid tumors and hematological malignancies (**Table 1**). From all monoclonal antibodies, there are only three biosimilar products marketed (bevacizumab, rituximab, trastuzumab; **Table 2**).

Monoclonal antibody	Approval date		Mechanism of action	Indication in oncology
	EMA ^a	FDA ^b		
Bevacizumab	2005	2004	Inhibition of vascular endothelial growth factor binding to the cell surface receptors	Metastatic colorectal cancer; unresectable, locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; hepatocellular carcinoma
Cetuximab	2004	2004	Competitive inhibition of the binding of epidermal growth factor	Metastatic colorectal carcinoma
Rituximab	1998	1997	Binding to B-lymphocyte antigen CD20 on the surface of B cells and activating the antibody-dependent cellular cytotoxicity and apoptosis	Non-Hodgkin's lymphoma; lymphocytic leukemia
Trastuzumab	2000	1998	Binding to the human epidermal growth factor 2 (HER2) will result in inhibition of the proliferation and survival of the cell	HER2-overexpressing breast cancer; HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

Legend: EMA, European of Medicines Agency; FDA, United States Food and Drug Administration; INN, international nonproprietary name.

^aAvailable at: www.ema.europa.eu.

^bAvailable at: www.accessdata.fda.gov.

Table 1.
First monoclonal antibodies used in oncology.

Monoclonal antibody	European of Medicines Agency ^a		Food and Drug Administration ^b	
	Trade name	Approval date	Trade name	Approval date
Bevacizumab	Mvasi	2018	Mvasi	2017
	Zirabev	2019	Zirabev	2019
	Equidacent	2020		
	Aybintio	2020		
	Onbevzi [*]	2020		
	Alymsys [*]	2021		
	Oyavas [*]	2021		
Rituximab	Truxima	2017	Truxima	2018
	Riximyo	2017	Ruxience	2019
	Blitzima	2017	Riabni	2020
	Rixathon	2017		
	Ritemvia	2017		
	Ruxience	2020		

Monoclonal antibody	European of Medicines Agency ^a		Food and Drug Administration ^b	
	Trade name	Approval date	Trade name	Approval date
Trastuzumab	Ontruzant	2017	Ogivri	2017
	Trazimera	2018	Herzuma	2018
	Kanjinti	2018	Kanjinti	2019
	Ogivri	2018	Ontruzant	2019
	Herzuma	2018	Trazimera	2019
	Zercepac	2020		

^aAvailable at: www.ema.europa.eu.

^bAvailable at: www.fda.gov/drugs/biosimilars/biosimilar-product-information.

^cThe product received the recommendation of the granting of marketing authorization.

Table 2.
 Biosimilar monoclonal antibodies with marketing approval for cancer treatment (until February 2021).

2. Development of monoclonal antibodies

Monoclonal antibodies consist in homogenous preparations of antibodies – or fragments of antibodies – in which every antibody in the product is identical in its protein sequence. All antibodies should have the same antigen recognition site, affinity, biological interactions, and downstream biological effects [2].

There are four types of monoclonal antibodies [9]:

- Murine: entirely derived from a murine source (hybridoma technology).
- Chimeric: the variable regions are of murine origins whereas the constant regions are human.
- Humanized: mostly derived from a human source except for the part of the antibody which binds to its target.
- Human: entirely derived from a human source

In summary, the traditional murine hybridoma technique starts by immunization of mice with desired antigens to trigger an immune response. Harvested splenocytes are fused with myeloma cells to produce hybridoma cells that persistently secrete the antibodies of interest. After the screening, selected leads are used to generate chimeric or humanized antibodies [9].

The main concern with this approach is the risk that might result in an immune response to the mouse antibody sequence. The consequence of this include allergic response and/or reduced bioavailability of mouse monoclonal antibodies. This immune response limited their clinical use [10].

Changes in the source of the molecule were determined as a solution to avoid the immune response. Introducing engineer changes, for example, recombinant DNA technologies, originated the chimeric, humanized, and human antibodies. Humanized mice allow for development of monoclonal antibodies with amino acid substitutions that lack mouse heavy chains and make them more similar to the human sequence system [2, 9].

The first chimeric antibody was approved in 1994 by the United States Food and Drug Administration (FDA) for inhibition of platelet aggregation in cardiovascular

diseases. The drug was developed by combining sequences of the murine variable domain with human constant region domain. In 1997, the first monoclonal antibody, rituximab – an immunoglobulin type 1 anti-CD20 -, was approved for non-Hodgkin's lymphoma by the FDA [9]. And the first humanized monoclonal antibody approved by the FDA also in 1997 was daclizumab, an anti-IL-2 receptor used for the prevention of transplant graft rejection [11].

Human monoclonal antibodies can either be obtained by phage display or transgenic animals [9]. Based on these techniques, the first fully human therapeutic antibody based on phage display was adalimumab, an anti-tumor necrosis factor α human antibody. It was approved in 2002 by the FDA for rheumatoid arthritis. Panitumumab, a monoclonal antibodies anti-epidermal growth factor receptor was the first human antibody generated in a transgenic mouse, approved by the FDA in 2006 and indicated for metastatic colorectal carcinoma, a type of cancer [11].

3. Biosimilar monoclonal antibodies in oncology

As mentioned before, three biosimilar monoclonal antibodies are available in oncology: bevacizumab, rituximab, and trastuzumab. Cetuximab is in preliminary steps of developing a biosimilar.

Bevacizumab is a humanized inhibitor of vascular endothelial growth factor (VEGF) monoclonal antibody. It acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors, which results in a reduction of microvascular growth of tumor blood vessels, reducing the blood supply to tumor tissues. Other results observed are decrease interstitial pressure on tissues, increase vascular permeability, induction of apoptosis of tumor endothelial cells, and may increase delivery of chemotherapeutic agents [12].

Rituximab is a chimeric monoclonal antibody that has a high-affinity binding to B-lymphocyte antigen CD20 (CD20) on the surface of B cells. The death of B cells occurs by different ways, including antibody-dependent cellular cytotoxicity (ADCC) and apoptosis [13].

Trastuzumab is a recombinant humanized monoclonal antibody that binds to the domain of the extracellular segment of the human epidermal growth factor-2 receptor (HER2), and inhibits the proliferation and survival of HER2-dependent tumors [14]. When trastuzumab is binding to HER2 receptor might occur the degradation of the receptor, attraction of immune cells to tumor cells by ADCC and inhibition of some pathways involved in the suppression of cell growth and proliferation [15].

4. Assessment of biological activity of biosimilar monoclonal antibodies

The biosimilar needs to demonstrate the proposed product is highly similar to the reference biological product and this is determined through a pathway that include comparative characterization made by evaluation of physicochemical, functional, and clinical characteristics of a biological product [16, 17].

The first step in biosimilar analytic characterization is identifying the characteristics associated with the quality, safety, and efficacy of reference biological product. These characteristics are known as critical quality attributes (CQAs) and represent physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [18].

Analytic testing of CQAs is performed to detect differences in factors such as the expression system, the manufacturing process, physicochemical properties, functional activities, receptor binding, immunochemical properties, impurities, and clinical outcome of the biosimilar candidate [19, 20].

It may be useful to compare the quality attributes of the proposed biosimilar product with those of the reference product using a meaningful fingerprint-like analysis. It means the results obtained are extremely sensitive in identifying analytical differences and allow a very high level of confidence in the analytical similarity of the proposed biosimilar product [21].

Once the CQAs for the biosimilar candidate are identified, the next step is to categorize the relative importance or criticality of each attribute. In the case of monoclonal antibodies, that are more complex biological products, determining criticality may be more challenging due to the increased number of attributes to evaluate and the potential impact of each difference on the desired product [22].

Significant differences for a very important CQA of the biosimilar candidate, such as the primary amino acid structure, are enough to interrupt the biosimilarity pathway. The manufacturer will need change their process to reach the high level of similarity between this structure in the biosimilar compared with the reference product. In the other hand, differences detected among CQAs of very low importance, such as minor modifications in amino acid side chains, may be acceptable if they can be justified or understood as clinically irrelevant [22, 23].

Primary amino acid structure is the core DNA sequence, and it must be exactly the same for the biosimilar product and the reference product [22]. There are a range of methods commonly used for evaluating the primary structure, including the peptide mapping, characterization of disulfide linkages, and glycosylation [24]. If the amino acid sequence is not identical, it can happen unwanted amino acid interactions that will impact in the safety, efficacy, and immunogenicity of the product [22].

Antibody molecules are molecules consisting of three equalized portions, constructed in the same way from paired heavy and light polypeptide chains that consists of a series of similar, sequences, each about more than a hundred amino acids long [25].

Changes in the protein can occur during any step of the manufacturing process, for example, enzymatic modifications, aggregation, variable glycosylation, etc. These modifications are named as post translational modifications. They can influence the physicochemical and biological properties of a protein and affect immunogenicity, immune response, and clinical efficacy [26]. In general, proteins can differ in at least three ways: (i) primary amino acid sequence; (ii) modification of amino acids, such as glycosylation or other side chains; and (iii) higher order structure [23]. Glycosylation and phosphorylation can impact on the efficacy and safety of a protein, for this reason, during the development process, they are extensively tested [22].

When the primary amino acid structure and the three-dimensional structure are reached in the biosimilar product, the correct protein arrangement and structural integrity are obtained and then, the ability of the biological product to bind to the target receptor will result in pharmacologic action. For this reason, target binding is considered a very highly CQA [27].

Impurities can be product – or process-related, arising from cell substrates or cell culture component [28]. They have the potential to affect all aspects of the product's profile [22]. For this reason, the chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities [28].

Because the quality attributes of a biosimilar are not identical to those of the reference product, in addition to the analytic package, animal toxicology,

pharmacokinetic and pharmacodynamic testing, and immunogenicity studies are required by the regulatory agencies for demonstrating biosimilarity [29]. Then, to ensure that these differences do not lead to any clinically meaningful differences, comparative clinical studies are performed [30]. It is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference product in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blinded and appropriate endpoints chosen [19].

5. Requirements for biosimilar monoclonal antibody clinical trials

Since the first monoclonal antibody have come off patent protection, regulatory agencies like European of Medicines Agency (EMA), FDA, Health Canada, Australian government Therapeutic Goods Administration (TGA) as well as the World Health Organization (WHO), developed guidance to manufactures interested in submitting applications for biosimilar products approval. Principles for designing, conducting, and reporting the results from clinical trials are set by these guidelines.

Clinical pharmacology studies are a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product [21].

The comparison of the pharmacokinetics properties of the biosimilar and the reference product forms the first step of a biosimilar monoclonal antibodies' development [29]. It is critical to use the appropriate bioanalytical methods to evaluate pharmacokinetics and pharmacodynamics properties [21]. They need to be accurate, precise, specific, sensitive, and reproducible.

The design of the study depends on some factors, including clinical context, safety, and the pharmacokinetics characteristics of the antibody [29]. Two study designs are of particular relevance: single dose crossover designs and parallel study designs. For pharmacokinetics similarity assessments, a single dose study, randomized, crossover study in healthy volunteers, is generally preferred [21, 29].

Pharmacokinetics and pharmacodynamics studies of trastuzumab (CT-P6 drug) [31] and bevacizumab (SB8 drug) [32] were developed with healthy participants. On the other hand, rituximab (PF-05280586) [33] were conducted with patients (rheumatoid arthritis or lymphoma). A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less pharmacokinetics and/or pharmacodynamics variability compared with a study in patients with potential confounding factors [21].

Single dose study is recommended for a product with a short half-life, a rapid pharmacodynamics response, and a low anticipated incidence of immunogenicity [21]. To biological products with a long half-life, e.g., the mean serum half-life of rituximab is 59.8 hours after the first infusion [34], to evaluate clinical pharmacokinetics and pharmacodynamics similarity, a parallel group design is more appropriate for this kind of product [21, 29].

To demonstrate comparable clinical efficacy of the biosimilar and the reference product, an adequately powered, randomized, parallel group comparative clinical trial, preferably double-blind, by using efficacy endpoints is usually necessary [19].

Confirmatory trials (superiority trials) for new drugs should demonstrate that the investigational product provides clinical benefit. In this way, FDA and EMA have published guidance to applicants, providing background information and general regulatory principles for cancer clinical trials [7, 35]. Acceptable primary clinical endpoints in this kind of trial include cure rate, overall survival (OS), progression free survival (PFS), disease free survival (DFS) [7, 35].

While clinical trials of originator products aim to demonstrate patient benefit, in the biosimilar comparable studies the intention is to compare the biosimilar product with the reference product to exclude clinically relevant product-specific differences [36]. In this case, the most appropriate study design is the equivalence study, and in some specific cases, non-inferiority trial may be accepted after to discuss with regulatory authorities [19, 23, 29]. For this, the manufacturer needs justify on the basis of a strong scientific rationale.

OS is considered the most reliable cancer endpoint because is precise, easy to measure and the bias is not a factor to worried. It is defined as the time from randomization until death from any cause. It is measured in the intent-to-treat population [29, 35]. As it is necessary to perform the study with long follow-up periods in large trials, this endpoint is not usually expected to be present in the biosimilar studies and it is not required by the regulatory agencies.

In the comparable studies, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorization application of the reference product [19, 37]. However, EMA advises to include some common endpoints to facilitate comparisons to the clinical trials conducted with the reference product [19].

At moment, a large number of studies with bevacizumab, rituximab and trastuzumab biosimilar are using the ORR as the primary endpoint, and EFS, PFS as the secondary endpoint (**Table 3**). OS is less frequently used.

ORR is defined by the regulatory agencies as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. The FDA has defined ORR as the sum of partial responses plus complete responses (CRs) [35]. ORR is a direct measure of a drug antitumor activity and should be assessed using a standardized criterion to determine the response [35]. The most common is the Response Evaluation Criteria in Solid Tumors (RECIST) guideline [55].

Beyond the pharmacokinetics and pharmacodynamics analyses, and clinical results, immunogenicity data should be collected and evaluated too. The goal is to investigate presence of an immune response to the therapeutic protein and its clinical impact [56].

The risk of immunogenicity varies between products and product categories, as well, between individuals and patient groups [56]. The consequences of an immune reaction to a therapeutic protein range from transient presence of anti-drug antibody (ADA) without any clinical significance to severe life-threatening conditions [56]. Immune responses to therapeutic protein products have the potential to affect product pharmacokinetic, pharmacodynamics, safety, and efficacy [56, 57].

When an ADA binds to or near the active site of a therapeutic protein or induces conformational changes, binding to relevant receptors will not happen and it will affect efficacy of the product. Besides these conformational-based effects, in addition immune-based adverse effects can happen. This includes injection-site and infusion reactions [56].

Among the product-related factors we have the protein origin (e.g. human or animal) and nature of the active substance (endogenous protein, post-translational modifications), significant modifications in the molecule structure, process-related impurities, formulation (excipients) and the interactions between the drug and/or formulation with the primary product packaging [56].

Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards [56, 58]. Assays used to detect antibodies against monoclonal antibody are often more problematic, difficult and can be technically challenging than for other proteins less complex [59].

Monoclonal antibody	Trade name	Study name or ID	Study design	Population and sample size (N)	Primary endpoint
Bevacizumab	Mvasi [38]	20120265	Non-inferiority study, randomized, double-blind, parallel, randomized	unresectable, locally advanced, or metastatic non-small cell lung cancer (642)	ORR
	Zirabev [39]	B7391003	Equivalence study, double-blind, parallel, randomized	unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (719)	ORR
	Equidacent [40]	FKB238-002	Equivalence study, double-blind, parallel, randomized	Newly diagnosed advanced (stage IV) / recurrent NS-NSCLC (731)	ORR
	Aybintio [41]	SB8-G31-NSCLC	Equivalence study, double-blind, parallel, randomized	Metastatic or recurrent nonsquamous Non-small Cell Lung Cancer (763)	ORR
Rituximab	Onbevzi	No information for public access			
	Alymsys				
	Oyavas				
	Riabni [42]	20130109	equivalence study, randomized, double-blind, parallel	low tumor-burden follicular lymphoma (256)	ORR
	Ruxience [43]	REFLECTIONS B328-06	equivalence study, randomized, double-blind, parallel	low tumor burden follicular lymphoma (394)	ORR
	Truxima [44]	CT-P10 3.3	non-inferiority, randomized, double-Blind, parallel	Advanced Follicular Lymphoma (121)	ORR
	Riximyo [45]	GPI3-301	Equivalence study, randomized, double-blind, parallel	previously untreated, advanced stage follicular lymphoma (629)	ORR
	Blitzima [46]	CT-P10 3.3	non-inferiority, randomized, double-blind, parallel	Advanced Follicular Lymphoma (121)	ORR
	Rixathon [47]	GPI3-301	Equivalence study, randomized, double-blind, parallel	previously untreated, advanced stage follicular lymphoma (629)	ORR
	Ritemvia [48]	CT-P10 3.3	non-inferiority, randomized, double-blind, parallel	Advanced Follicular Lymphoma (121)	ORR

Monoclonal antibody	Trade name	Study name or ID	Study design	Population and sample size (N)	Primary endpoint
Trastuzumab	Ogivri [49]	MYL-Her-3001	equivalence study, randomized, double-blinded, parallel	metastatic breast cancer (458)	ORR
	Trazimera [50]	B3271002	equivalence study, randomized, double-blind, parallel	metastatic breast cancer (707)	ORR
		B3271004	non-inferiority study, randomized, double-blind, parallel	operable breast cancer (226)	pCR
	Kanjinti [51]	20120283	equivalence study, randomized, double-blind, parallel	operable breast cancer (725)	pCR
	Ontruzant [52]	SB3-G31-BC	equivalence study, randomized, double-blinded, parallel	operable breast cancer (875)	pCR
	Herzuma [53]	CT-P6 3.2	equivalence study, randomized, double-blind, parallel	operable breast cancer (549)	pCR
	Zercepac [54]	HLY02-BC01	equivalence study, randomized, double-blind, parallel	metastatic breast cancer (649)	ORR

Legend: ORR, overall response rate; pCR, pathological complete response.

Table 3.
 Study design and primary endpoint for biosimilar monoclonal antibodies for cancer treatment.

Finally, when all tests are done and the authorization holder will submit the documents to receive the marketing authorization, it can be extrapolating all indications from the reference product to the biosimilar. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable but needs to be scientifically justified. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated in all aspects described before [19, 23, 29].

This condition is not applied in all situations. For example, if a reference monoclonal antibody is licensed both as an immunomodulator and as an anticancer antibody, the scientific justification as regards extrapolation between the two indication is more challenging and may have to involve more specific studies [29].

6. Conclusions

Since monoclonal antibodies play an essential role in cancer treatment and are responsible for high healthcare costs, the development of biosimilars is particularly important in oncology. Several biosimilars of the monoclonal antibodies trastuzumab, rituximab, and bevacizumab have been approved and began to be marketed in Europe, EUA and other countries around the world. More diversification of monoclonal antibodies biosimilars is expected in the next years, as the patent of other molecules will expire.

The biosimilar development pathway consists of a comprehensive comparability exercise between the biosimilar candidate and the reference product, primarily focusing on data from analytical studies. Clinical studies for biosimilar candidates follow a different design to those for a new biological. Adequate information on the biosimilar approval pathway, the robustness of overall evidence used to demonstrate biosimilarity, and how the clinical development of a biosimilar is done is important for all: professional, patient, governments, and other stakeholders.

Conflict of interest

Annemeri Livinalli: is involved in consulting, advisory work and speaking engagements for Amgen, Sandoz, Teva, Servier, Dr. Reddy's, Accord, United Medical, Achè.


Taís Freire Galvão: The author declares no conflict of interest.

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Biosimilar Monoclonal Antibodies in Latin America

Paola Karp, Matías Gatto, María Victoria Batto, Sol Ferrero and Gustavo Helguera

Abstract

In the last decade, the expiration of patents protecting therapeutic monoclonal antibodies opened an opportunity for the development and approval of biosimilar versions of these drugs. The complexity of these biologic molecules required the imposition of strict regulations to establish robust comparability with the antibody of reference in physicochemical, analytical, biological and, when deemed necessary, clinical data. Accordingly, this period coincides with the updating of the requirements and guidelines for the manufacture and approval of biologics in Latin American countries by their respective regulatory agencies. Although the term “biosimilar” does not appear in the official regulatory provisions in most of the countries, it is of general use in Latin America, and several biosimilars of therapeutic monoclonal antibodies were approved based on comparative quality, nonclinical and clinical data that demonstrate similarity to a licensed biological reference registered before in a Regulatory Health Authority of reference. Here, we provide an overview of how the complexities of therapeutic monoclonal antibodies shaped the regulatory landscape of similar biologics, the current status of biosimilar monoclonal antibodies in Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, México, Paraguay, Perú and Uruguay and their potential to reduce the cost of antibody therapies in this region.

Keywords: monoclonal antibody, biosimilar, biologics, Latin America, Argentina, Brazil, Chile, Colombia, México, Perú

1. Introduction

1.1 The evolution of monoclonal antibodies to biologic medicines

Antibodies, also known as immunoglobulins, are complex glycoproteins produced by B-cells against foreign substances as part of the adaptive immune response [1, 2]. The invention of the hybridoma technology in 1975 by Köhler and Milstein allowed the production of monoclonal antibodies with a desired specificity from a unique clone of B cells [3]. In contrast to polyclonal antibodies, monoclonal antibodies are homogeneous, monospecific, and could be produced in unlimited quantities in the laboratory. Since they can be directed against almost any molecular epitope, monoclonal antibodies were early adopted as a diagnostic tool, but took more than a decade until the approval of Muromonab-CD3 (Orthoclone Okt3®), which is the first monoclonal antibody developed with the hybridoma technology commercialized for therapeutic use [4]. However, since antibodies from hybridoma technology

have only murine sequences, in human patients they exhibited limited effector function [5], were immunogenic inducing anti-mouse antibodies, and had a significantly reduced half-life [6]. Therefore, it was not until the development of recombinant monoclonal antibodies in the 1980s and 1990s that a new era of biologic therapy began, with the chimerical [7], humanized [8] and fully human antibodies [9]. Each step involved the gradual replacement of murine segments of the antibody sequence by the corresponding human sequence: in chimeric antibodies the constant region was replaced, and in humanized antibodies, the framework flanking the complementarity-determining regions and the constant region were replaced, and in human monoclonal antibodies the whole sequence is human. Further engineering allowed their customization, creating variants in valence, size, effector functions and with the conjugation of compounds for delivery to targeted cell types such as cancer.

1.2 The emergence of biosimilar antibodies and Latin America

In the last twenty years, therapeutic monoclonal antibodies have been increasingly and consistently approved and by 2021 it is estimated that 106 monoclonal antibodies would have been approved in the United States or European Union for treatment of an expanding spectrum of diseases [10]. The emergence of next-generation therapeutic monoclonal antibodies in the last decade coincides with the expiration of the patents protecting the early recombinant monoclonal antibodies [11]. The approval in 2013 of the infliximab biosimilar Remsima® [12] opened an emerging field of competition all over the world, with the development of biologic copies that exhibit equivalent quality and efficacy compared to the original antibodies. It was also an opportunity for biopharmaceutical companies in Latin America to enter this market, encouraged also by their governments. However, monoclonal antibodies post-translational modifications include different degrees of glycosylation, disulphide bridge variants, or C/N terminal modifications that are dependent on the manufacturing process [13]. Because of this structural complexity, regulatory agencies in Latin America went through profound changes in their standards in order to update the criteria for evaluation and approval of antibody biosimilars, requiring comparability analysis in safety and efficacy. Today, their requirements usually include the provision of detailed physicochemical, pharmaceutical, and biological information regarding critical quality attributes of the active principle and the manufacturing process. In addition, the comparability also requires establishing if there are variations in the type of host cell to produce of the recombinant protein, the amino acid sequence, the secondary, tertiary, and quaternary structure, interactions, post-translational modifications, the formulation, as well as impurities related to the process or storage. The challenge for their approval by regulatory agencies is reshaping the accessibility of these expensive medicines in Latin America. Here we focus our analysis on biosimilars that have been characterized in their physicochemical properties and showed evidence of quality, efficacy and safety published in the scientific literature, and will not include products known as copies or intended copies whose sponsors have failed to present sufficient evidence of their equivalence to the product of reference.

1.3 Regulation of biosimilars in Latin America

Aiming to meet the international standards for production and development of biologic medicines, since 2008, Latin American countries began joining the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and today Argentina, Brazil and Mexico are members. This organization sets standards in the international development, implementation and maintenance of harmonized Good

Manufacturing Practices (GMP) and quality systems of inspectorates of medicinal products. Only these three countries in Latin America have developed a biotechnology industry that include private companies with the capacity to manufacture biologic medicines. Meanwhile, today most countries in Latin America have approved specific regulations for the registry of biologic medicines and of similar biotherapeutic products or biosimilars. The World Health Organization uses a definition for these medicines as “biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product” [14]. As expected, each country in Latin America has adopted its own regulatory framework for the registration and approval of biosimilars.

The registration of biosimilar medicines in Argentina is controlled by the National Administration of Drugs, Foods and Medical Devices (Administración Nacional de Medicamentos Alimentos y Tecnología Médica, ANMAT). In 2011 was published provision N° 7729/2011, that “approved the requirements and guidelines for the registration of medicinal specialties of biological origin whose qualitative-quantitative composition, therapeutic indication and proposed route of administration, have precedents in other medicinal specialties of biological origin authorized and registered before this Administration or another Regulatory Health Authority (medicine biological reference or comparator), of which there is evidence of effective commercialization and sufficient characterization of its risk-benefit profile” [15]. The term “biosimilar” is not used in any of the regulatory provisions of ANMAT approved to date [16], referring to these products as “similar biological medicines”.

In Brazil, the National Health Surveillance Agency (Agencia Nacional de Vigilância Sanitária, ANVISA) is the registry agency in charge of the approval of the biosimilars, which is regulated under the resolution RDC 55/2010 [17, 18]. Although ANVISA does not use the term “biosimilar” in its resolution, its definition is merged with the term “biological product”, which is defined as the non-new or known biological medicine that contains a molecule with known biological activity, already registered in Brazil and that has gone through all manufacturing steps (formulation, filling, lyophilization, labelling, packaging, storage, quality control and release of the batch of biological product for use) [17]. The approval of these biological products will require comparability studies with a biological comparator with regard to non-clinical and clinical parameters based on quality, efficacy and safety, in order to establish that there are no detectable differences in terms of quality, efficacy and safety between the products. The biological drug of reference or innovator receives the name of “new biological medicine”, and the product of reference “comparator biological product” is a biological product that has already been registered with ANVISA on the basis of a complete dossier and has already been marketed in the country.

The National Medicines Agency (Agencia Nacional de Medicamentos, ANAMED) is the regulatory agency in Chile that regulates the technical standard for sanitary registration of biotechnological products derived from recombinant DNA techniques. In their regulatory technical norm for biologic medicines, the term biosimilar is defined as “the biotechnological medicine that has been shown to be comparable in quality, safety and efficacy to the reference biotechnological product, based on its exhaustive characterization through comparability studies under equal conditions, consisting of quality studies and non-clinical and clinical studies, all of them comparative” [19, 20].

The regulatory agency responsible for the approval of biologic medicines in Colombia is the National Drug and Food Surveillance Institute (Instituto Nacional de Vigilancia de Medicamentos y Alimentos, INVIMA). In 2014, the Decree N° 1782 [21] that describes the registration pathway for biosimilars in that country was published. Even though the directive does not use the term “biosimilar”, it refers to them as “similar biotherapeutic products” and established a specific regulatory system for their registry. This application requires a series of tests comparing the

attributes of quality, safety and efficacy between the biosimilar and the biologic reference medicine to demonstrate that the drug under evaluation is highly similar to the reference drug [21].

The regulation of biologic medicines in Ecuador is overseen by the Regulatory, Control and Surveillance National Agency (Agencia Nacional de Regulación, Control y Vigilancia Sanitaria, ARCSA). The Health Ministry approved in 2019 the agreement 385 that regulates the commercialization of biological medicines for human use and consumption in Ecuador, as well as to establish the general procedure for obtaining the Sanitary Registry. In this directive, the biosimilars are defined as a biological medicinal product that has been shown by the comparability exercise to be similar in terms of quality, safety and efficacy to the reference biological medicinal product [22, 23].

Mexico is another country where the term “biosimilar” is not used in their regulatory norms for approval of biologic medicines. The Federal Commission for Sanitary Risks Protection (Comisión Federal para la Protección contra Riesgos Sanitarios, COFEPRIS) is the agency in Mexico responsible for regulating the approval, manufacture and commercialization of biologic medicines. The norm NOM-257-SSA1-2014 establishes the regulatory framework for biotechnological medicines and refer to “biocomparable biotechnological medicine”, as the non-innovative biotechnological medicine that proves to be comparable in terms of safety, quality and efficacy of the reference biotechnological medicine through biocomparability studies [24, 25].

The registration of biological medicines in Paraguay is regulated by the National Directorate for Sanitary Surveillance (Dirección Nacional de Vigilancia Sanitaria, DINAVISA). The Decree N° 6611 approved in 2016 established the requirements for the approval of biologic medicines and includes the definition for similar biologic medications or biosimilars [26]. In this decree, biosimilars are defined as a biological medicine product that demonstrates similarity in terms of safety, quality, efficacy and immunogenicity to the reference biological medicinal product through the comparability exercise [26].

In Peru, the General Directorate of Pharmaceuticals, Devices and Drugs (Dirección General de Medicamentos, Insumos y Drogas, DIGEMID) is the agency in charge of the regulations and norms regarding approval and certification of biologic medicines. In 2016 the Supreme Decree N° 013-2016-SA that regulates the registration of biological products, which choose the path of similarity, or similar biologic products was approved [27]. In this norm, they are defined as the biological product, which in terms of quality, safety and efficacy, is similar to a biological reference product [27].

Most of the remaining countries in Latin America do not have dedicated agencies or specific norms that regulate the approval and surveillance of biosimilars, and therefore will not be included in this analysis [25].

2. Biosimilar monoclonal antibodies approved in Latin America

Currently there are five therapeutic monoclonal antibodies registered in Latin America whose patents expired in recent years and have biosimilar versions commercialized in the region (**Figure 1**). Those are rituximab, trastuzumab, infliximab, adalimumab and bevacizumab, and only Argentina, Brazil and Colombia have at least one biosimilar version approved for each monoclonal antibody (**Figure 1**). With more than ten biosimilars approved, Argentina and Brazil are the countries in Latin America with more biosimilar monoclonal antibodies approved. Next are Colombia, Peru, Paraguay, Mexico and Chile, with 3 to 5 biosimilars of monoclonal antibodies, and the lowest adoption of biosimilars is in Ecuador, Bolivia and Uruguay

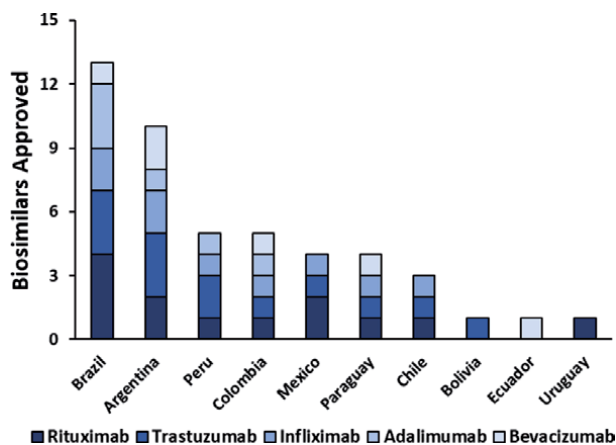


Figure 1.
Comparative plot of the number of biosimilars approved in Latin American countries.

(**Table 1** and **Figure 1**). Recent reports indicate that in Brazil the prices in U.S. dollars of original biologics, including therapeutic monoclonal antibodies, have been declining significantly in the last decade. The emergence of competition by biosimilars, with their lower prices may strengthen this trend [28]. It is expected that the approval of more biosimilar monoclonal antibodies will increase the competition, decreasing the healthcare costs and expanding the accessibility of this class of drugs.

2.1 Rituximab

Developed by Genentech in the United States, rituximab is marketed with the brand name Rituxan® (also known as MabThera®) and is currently commercialized by Roche. Rituximab is a murine/human chimeric monoclonal antibody with IgG1 / κ isotype directed against the CD20 antigen expressed by B cells used for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) [29], and rheumatoid arthritis [30]. Rituximab was approved by the FDA in 1997 for the treatment of B-cell Lymphomas and was the first chimeric recombinant monoclonal antibody approved against cancer. Several biosimilars of rituximab have been developed over the years, and by 2021 there are five different biosimilars of rituximab approved in Latin America, with nine different brand names commercialized in Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Paraguay, Peru and Uruguay (**Table 1**).

2.1.1 Ruxience® (Pfizer)

PF-05280586 (Ruxience®) is a biosimilar of rituximab developed in the United States by Pfizer and commercialized in Brazil as Ruxience® by Wyeth Industria Farmaceutica. It is a monoclonal antibody used in the treatment of various types of cancer and immunological indications. In Brazil, PF-05280586 was approved with the same therapeutic indications approved for the reference rituximab.

Comparative biochemical and functional characterization were carried out to determine the level of physiochemical similarity, tryptic peptide maps were generated for both PF-05280586 and rituximab-EU and resolved by reverse-phase high-performance liquid chromatography Ryan [31]. This study proved that PF-05280586 has an identical primary amino acid sequence to rituximab. Additionally, it was demonstrated to be highly similar based on the comparison of physicochemical critical attributes, and non-clinical *in vitro* functional characteristics [31].

Non-proprietary name	Antibody name	Brand name (country)	Manufacturer (country)	Distributor (country)
Rituximab		#Rituxan® / #Mabthera®	Roche (SW)	Roche
	PF-05280586	Ruxience® (BR)	Pfizer (US)	Wyeth (BR)
	RTXM83	Novex® (AR, PA, UR) Rigetuxer® (ME)	mAbxience (AR)	Laboratorios Elea (AR) Laboratorios PISA (ME) Laboratorios Bioéticos (PA) Urufarma (UR)
		Vivaxxia® (BR)	Libbs (BR)	Libbs (BR)
	GP2013	Rixathon® (AR) Riximyo® (BR) Arasamila® (ME)	Sandoz (AU)	Novartis (AR) Sandoz (BR, ME)
	CT-P10	Truxima® (BR, CH, CO)	Celltrion (SK)	Celltrion (BR, CO) Saval (CH)
	Zytux	Zaytux® (PE)	AryoGen (IR)	PeruLab (PE)
Trastuzumab		#Herceptin®	Roche (SW)	Roche
	ABP 980	Kanjinti® (AR, PE)	Amgen (US)	Varifarma (AR, PE)
	MYL-14010	Ogivri® (CO) Tuzcepta® (AR) Zedora® (BR) Bisintex® (BO, CH, PA, PE)	Biocon (IN)	Laboratorios Raffo (AR) Libbs (BR) PharmaTech Boliviana (BO) Recalcine (CH) Mylan (CO) Pharma International (PA) Abbott (PE)
	PF-05280014	Trazimera® (AR, BR)	Pfizer (US)	Pfizer (AR) Wyeth (BR)
	CT-P6	Herzuma® (BR)	Celltrion (SK)	Celltrion (BR)
Infliximab		#Remicade®	Janssen (US)	Janssen
	CT-P13	Remsima® (AR, BR, CH, CO, EC, ME, PA) Flixceli® (PE)	Celltrion (SK)	Gobbi-Novag (AR) Celltrion (BR, CO, ME, PA) Saval (CH) Oxialfarm (EC) AC Pharma (PE)
	PF-06438179 / GP1111	Ixifi® (AR) Xilfya® (BR)	Pfizer (US)	Pfizer (AR) Wyeth (BR)
Adalimumab		#Humira® / #Trudexa®	AbbVie (US)	AbbVie
	ABP 501	Amgevita® (AR, BR, CO, PE)	Amgen (US)	Amgen (AR, BR, CO) TecnoFarma (PE)
	GP2017	Hyrimoz® (BR)	Sandoz (GE)	Sandoz (BR)
	PF-06410293	Xilbrilada® (BR)	Pfizer (US)	Wyeth (BR)
Bevacizumab		#Avastin®	Roche (SW)	Roche
	BEVZ92	Bevax® (AR, EC, PA)	mAbxience (AR)	Laboratorios Elea (AR) Grünenthal (EC) Laboratorios Bioéticos (PA)
	ABP 215	Mvasi® (AR, BR, CO)	Amgen (US)	Amgen (CO)

[#]Reference Monoclonal Antibodies. Countries: Argentina (AR); Austria (AU); Bolivia (BO); Brazil (BR); Chile (CH); Colombia (CO); Ecuador (EC); Germany (GE); India (IN); Iran (IR); Mexico (ME); Paraguay (PA); Peru (PE); Russia (RU); South Korea (SK); Switzerland (SW); Uruguay (UR); and United States (US).

Table 1.
Biosimilar monoclonal antibodies approved in Latin America.

In a randomized 3-way pharmacokinetic (PK) similarity study in subjects with active rheumatoid arthritis, PK equivalence was demonstrated between PF-05280586 and rituximab-EU, PF-05280586 and rituximab-US, and rituximab-EU and rituximab-US. This study also demonstrated comparable CD19-positive B cell depletion, pharmacodynamic (PD) responses, safety and immunogenicity profiles for all treatments [32–34].

A phase III study was carried out to compare the safety and effectiveness of PF-05280586 versus rituximab-EU in patients with CD20-positive, low tumour burden follicular lymphoma [35]. This study proved that the effectiveness of PF-05280586, as measured by the Overall Response Rate, is similar to that of rituximab-EU [35].

2.1.2 Novex® / Rigetuxer® / Vivaxxia® (mAbxience)

RTXM83 (Novex® / Rigetuxer® / Vivaxxia®) is a rituximab biosimilar developed in Argentina by PharmADN (today mAbxience) and is the first biosimilar therapeutic monoclonal antibody to be developed by a local biopharmaceutical company in Argentina. RTXM83 is commercialized in Argentina with the brand name Novex® by Laboratorios Elea. In Paraguay, RTXM83 is marketed as Novex® by Laboratorios Bioéticos, and in Uruguay it is also sold as Novex® by Urufarma. In Mexico, RTXM83 is commercialized with the brand name Rigetuxer® by Laboratorios PISA. In Brazil, RTXM83 is manufactured by Libbs and marketed by the same laboratory as Vivaxxia® [36, 37].

RTXM83 is authorized for NHL with clinical trial, and by extrapolation for the following therapeutic indications to CLL, rheumatoid arthritis, adult patients with Wegener's granulomatosis (GW) and microscopic polyanginitis (PSM).

Comparability studies have shown similar physicochemical properties between RTXM83 and reference rituximab in primary sequence and disulphide bonds, N-terminal and C-terminal amino acid modifications, thermal stability, charge variants, glycosylation pattern, presence of higher order aggregates, purity, and binding affinity to the neonatal receptor and other Fc receptors [38]. Further comparability studies of biological activity *in vitro* were performed, showing similarity in tests of potency of antibody-dependent cell mediated cytotoxicity (ADCC), and binding to the molecular target CD20 [39]. In addition, *in vivo* studies in cynomolgus monkeys showed similarity in pharmacokinetics (PK) including area under the concentration-time curve (AUC), maximum drug concentration and pharmacodynamics (PD) including the depletion of CD20 and CD40 cells [40].

Data from the phase III clinical trial NCT02268045 in patients with diffuse large B-cell lymphoma has shown similarity comparing the PK parameters in patients treated with RTXM83 and with reference rituximab (in both cases co-administered with cyclophosphamide, doxorubicin, vincristine, and prednisone - CHOP) [41]. In addition, PD was assessed in terms of CD20-positive and CD19-positive B-cell count depletion, length of suppression and time to recovery, with similar profile observed for both treatment arms [41]. In addition, the randomized, double-blind, phase III study comparing RTXM83 versus reference rituximab, both in combination with CHOP showed no obvious differences in the safety profile in terms of nature, frequency and severity of adverse events, and in efficacy in terms of tumour response. The immunogenicity was assessed as the incidence of anti-drug antibodies, which was low and similar between RTXM83 and reference rituximab, with $\leq 4\%$ in both arms [41].

ANMAT in Argentina has established a prospective Treatment Registry as part of its pharmacovigilance program for the detection, evaluation, understanding and prevention of adverse effects derived from the use of medicines, and in 2014, it started to collect data from patients treated with RTXM83. Physicians have sent

information to this registry between 2014 and 2017 from patients treated with RTX83 for Follicular NHL, diffuse large B-cell NHL, CLL and off-label clinical indications [42]. This active pharmacovigilance program of RTX83 allows the continuous monitoring of the safety profile of this biosimilar, and its 4% ICSR frequency is comparable to the safety profile of the reference product [42].

2.1.3 Rixathon®/Riximyo®/ Arasamila® (Sandoz)

GP2013 (Rixathon® /Riximyo®/ Arasamila®) is a rituximab biosimilar developed by Sandoz in Austria. GP2013 was registered in Argentina by Novartis with the brand name Rixathon®. GP2013 was registered by Sandoz in Brazil as Riximyo® and was also registered by Sandoz in Mexico with the brand name Arasamila®. It has been in clinical use for the treatment of patients with NHL, CLL, rheumatoid arthritis and other autoimmune conditions [43].

According to a physicochemical and functional comparability with the reference rituximab, GP2013 amino acid sequence and molecular mass were shown to be identical between them [44]. Furthermore, specific amino acid modifications and the glycan pattern were indistinguishable from originator rituximab [44]. The bioassays and the binding assays to measure the functionality revealed a similar result for the biosimilar and the reference antibody, especially the ADCC potency, which was tested *in vitro* and *in vivo* [44, 45]. The preclinical comparability exercise performed in cynomolgus monkeys revealed that pharmacokinetics and pharmacodynamics were comparable between GP2013 and reference rituximab [45].

A randomized double-blind clinical study was performed where patients with rheumatoid arthritis with inadequate response or intolerance to Tumor Necrosis Factor- α (TNF α) treatment received GP2013 or reference rituximab along with methotrexate and folic acid [46]. In this clinical trial, efficacy, safety and immunogenicity profiles were similar between GP2013 and originator rituximab, in addition to the equivalence showed in the pharmacokinetics and pharmacodynamics parameters [46].

Further studies of efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of GP2013 plus cyclophosphamide, vincristine and prednisone (GP2013-CVP) compared with reference rituximab were performed in a multinational, double-blind, randomized, phase III clinical trial in adults with previously untreated, advanced stage follicular lymphoma [47]. Equivalence of the global response was observed in the group with GP2013 (87%) compared with reference rituximab (88%) [47]. Based on primary and secondary efficacy outcomes, the equivalence between GP2013 and the reference rituximab in terms of overall response rate for tumour assessment, and similar complete response, partial response, stable disease and progressive disease, in patients with untreated, advanced stage follicular lymphoma was demonstrated [47].

The overall frequencies of common adverse events and serious adverse events were comparable between both treatment groups in follicular NHL (Combination and Maintenance phases) and in rheumatoid arthritis. The safety profiles including immunogenicity of GP2013 in the pivotal populations are consistent with the known safety profile of the reference medicine reported in clinical trials and post-marketing surveillance. Additionally, no safety risks were detected in patients who switched from the reference medicine to GP2013 [47].

2.1.4 Truxima® (Celltrion)

CT-P10 (Truxima®) is a biosimilar of rituximab developed by Celltrion Healthcare in South Korea. CT-P10 is commercialized with the brand name

Truxima® by Celltrion in Brazil and Colombia and by Saval in Chile. Truxima® was approved for the treatment of NHL, CLL, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis [48, 49].

CT-P10 has shown high similarity in its primary structure, higher-order structures, post-translational modifications and biological activities [50]. Biosimilarity of CT-P10 with the reference rituximab, was achieved with a 3-way similarity assessment conducted between CT-P10, EU-rituximab and US-rituximab, focusing on the physicochemical and biological quality attributes [50]. A multitude of analyses revealed that CT-P10 has identical primary and higher order structures compared to the original product. Purity/impurity profiles of CT-P10 measured by the levels of aggregates, fragments, non-glycosylated form and process-related impurities were also found to be comparable with those of reference medicinal product [50]. In terms of the post-translational modification, CT-P10 contains slightly less N-terminal pyro-glutamate variant, which has been known not to affect product efficacy or safety. Arrays of biological assays representative of known and putative mechanisms of action for rituximab have shown that biological activities of CT-P10 are within the quality range of reference rituximab [50].

A Phase I clinical trial was conducted to evaluate the pharmacokinetics of CT-P10 and reference rituximab. Results of the study demonstrated that CT-P10 and reference rituximab were statistically equivalent after a single course of treatment at week 24. The study also found that the efficacy, pharmacodynamics, immunogenicity and safety were similar up to two courses of treatments up to 72 weeks [51]. The results of another Phase I open-label extension clinical study demonstrated that switching to CT-P10 from reference rituximab was effective with comparable safety to continuing CT-P10 for two years [52].

Phase III comparative clinical trials on CT-P10 were carried out in patients with rheumatoid arthritis, advanced follicular lymphoma and low-tumour-burden follicular lymphoma (LTBFL) [52, 53]. The results showed that treatment with CT-P10 in rheumatoid arthritis patients resulted in highly similar efficacy, PK, PD, immunogenicity and safety profiles compared to those treated with reference rituximab [52]. CT-P10 also showed to be equivalent in terms of efficacy and safety in patients with LTBFL [53].

2.1.5 Zaytux® (AryoGen)

Zaytux®/Zytux® is a biosimilar of rituximab developed by AryoGen Biopharma in Irán and distributed in Peru by Perulab. It is used for treatment of adult patients with NHL, CLL, Rheumatoid Arthritis (RA) and Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

Comparability studies revealed similar physicochemical and biological properties between Zytux and reference rituximab [54]. Similar primary structure and post-translational modification were found. In addition, comparable secondary, tertiary and quaternary structures were obtained for the rituximab originator and biosimilar, analyzed by CD spectroscopy, NMR spectroscopy, FTIR and Ion mobility MS. Small differences in mass determination studies were found in biosimilar Zytux® with regard to reference rituximab; the most relevant are the incomplete truncation of the C-terminal lysine of heavy chains and a difference of 2 Da in light chains. Data has shown high similarity of N-glycan pattern and identity of the main glycoforms [54]. Batch-to-batch comparability assessment of released N-glycans from rituximab and its biosimilar showed that their N-glycan patterns are qualitatively similar, but quantitatively heterogeneous, although they are considered acceptable changes. Surface plasmon resonance-binding studies showed that the Fc binding of Zytux and rituximab to recombinant human Fc receptor and FcRn

receptor variants exhibit similar equilibrium constant (KD) values. Additionally, comparable results were obtained from binding assays to C1q and complement-dependent cytotoxicity (CDC) assays. Furthermore, binding assays between the antibodies and CD20 were performed and they showed similar affinities [54].

Data from clinical trials in CLL and NHL patients showed comparable outcomes in terms of efficacy and safety for Zytux® and reference rituximab [55]. CLL patients were included in a double-blind, randomized study that showed non-inferior and comparable results in terms of efficacy (overall response rate and B-cell specific markers) and safety (infusion reactions, hematologic toxicity and non-hematologic toxicity). Another study carried out in 10 CLL and 10 NHL patients evaluated the safety and efficacy of Zytux® in comparison with reference rituximab [56], concluding that Zytux® was not inferior to reference rituximab, and was comparable and even better in terms of safety and efficacy.

2.2 Trastuzumab

Developed by Genentech in the United States, trastuzumab is marketed with the brand name Herceptin® and manufactured by Roche. Approved by the FDA in 1998, trastuzumab was the first humanized monoclonal antibody against cancer. It is a humanized IgG1 / κ monoclonal antibody that targets the extracellular domain of the human epidermal growth factor receptor 2 (HER2) and is used for the treatment of HER2-positive early or metastatic breast cancer [57]. In 2021, there are a total of four different trastuzumab biosimilars approved in Latin America, with seven different brand names marketed in Argentina, Brazil, Colombia and Peru (Table 1).

2.2.1 Kanjinti® (Amgen)

ABP 980 (Kanjinti®) is a trastuzumab biosimilar developed in the United States by Amgen. ABP 980 was approved by the FDA for all approved indications of the reference product, including the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastro-esophageal junction adenocarcinoma. It was registered in Argentina and Perú as Kanjinti® by Varifarma S.A.

ABP 980 was proved to have a similar physicochemical and functional properties to those of reference trastuzumab, physicochemical is similar to reference trastuzumab in terms of primary and higher order structure, carbohydrate structure, kinetic binding properties (vs. both US- and EU-sourced reference trastuzumab) and purity [58–60]. Minor differences between the two agents were not considered clinically meaningful.

In a single-dose clinical study, the pharmacokinetic similarity of ABP 980 to both US- and EU- trastuzumab was demonstrated. No differences in safety and tolerability between treatments were noted and no subject tested positive for binding antibodies [61]. Additionally, pharmacodynamic was proven to be of similar potency to that of EU-sourced reference trastuzumab in terms of proliferation inhibition and induction of ADCC [59].

In the phase III LILAC clinical study, ABP 980 demonstrated similar clinical efficacy and tolerability to that of reference trastuzumab in patients with HER2-positive early breast cancer [62, 63]. In addition, the immunogenicity and safety profiles of ABP 980 were similar to those of reference trastuzumab, and a single switch from reference trastuzumab to ABP 980 had no impact on the immunogenicity or safety of ABP 980 [62]. Switching from trastuzumab to ABP 980 had no significant impact on event-free survival and did not adversely affect its tolerability [63]. Sensitivity analyses were carried out based on central laboratory evaluation of

tumour samples; estimates for the two drugs were contained within the predefined equivalence margins, indicating similar efficacy [62]. ABP 980 and reference trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study [62, 64].

2.2.2 *Tuzepta*® / *Zedora*®/ *Ogivri*®/ *Bisinte* ® (*Biocon*)

Known as MYL-1401O (*Tuzepta*®, *Zedora*®, *Ogivri*® and *Bisintex*®) this trastuzumab biosimilar was developed in India by Biocon / Mylan. It was approved by the FDA in 2017 and in the United States, it is marketed by Mylan with the brand name *Ogivri*®. MYL-1401O is indicated for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. In Argentina, MYL-1401O was registered as *Tuzepta*® by Laboratorio Raffo; in Brazil it was registered as *Zedora*® by Libbs; in Colombia it was registered as *Ogivri*® and distributed by Mylan. In Bolivia, Chile, Paraguay and Perú it is commercialized as *Bisintex*® and distributed by PharmaTech Boliviana in Bolivia, Recalcine in Chile, Pharma International in Paraguay and Abbott in Perú.

The totality of evidence for MYL-1401O supports its biosimilarity to reference trastuzumab based on a comparability exercise, including structural and functional analytic similarity assessments and a confirmatory clinical study [65, 66]. The comparability studies conducted for MYL-1401O and reference trastuzumab included a physicochemical stability study, where all storage conditions were tested. The results showed that there was no change in the tertiary structure of MYL-1401O as assessed by second-derivative ultraviolet and fluorescence-derived spectral analysis, and no evidence of oligomer formation or fragmentation was observed as assessed by gel exclusion chromatography and dynamic light scattering. Ion-exchange chromatography showed no significant changes in the distribution of ionic variants [67].

MYL-1401O was well tolerated and demonstrated pharmacokinetic and safety profiles similar to reference trastuzumab in healthy volunteers [68]. This was proved with a single-centre, randomized, double-blind, three-arm, parallel-group, phase I study conducted in healthy adult male volunteers who received MYL-1401O or reference trastuzumab as a 90-min intravenous infusion. The clinical study demonstrated that among women with HER2-positive metastatic breast cancer receiving taxanes, the use of MYL-1401O compared with reference trastuzumab resulted in an equivalent overall response rate at 24 weeks [66].

2.2.3 *Trazimera*® (*Pfizer*)

PF-05280014 (*Trazimera*®) is a trastuzumab biosimilar developed in the United States by Pfizer and approved in the European Union in 2018 [69]. It is indicated for the treatment of adult patients with HER2 positive metastatic breast and gastric cancer [70]. *Trazimera*® was registered in Argentina by Pfizer and in Brazil by Wyeth.

Physicochemical characterization was proved to be similar to reference trastuzumab (both EU and US sourced) in terms of primary, secondary and tertiary structures, post-translational modifications, charge variants, purity and stability [71]. No clinically significant differences between PF-05280014 and EU- and US-sourced reference trastuzumab were found following formulation changes (i.e., slight shift in total a fucosylation, terminal galactosylation and G0 species). Minor structural and functional differences between PF-05280014 and reference trastuzumab were not considered clinically relevant [71].

Pharmacodynamic properties of PF-05280014 were found to be similar to those of reference trastuzumab (both EU- and US-sourced) in terms of biological activity, including binding and functional characteristics (e.g., HER2 binding, C1q binding,

Fab- and Fc-based functions, ADCC and ADCP activities). Equivalent efficacy and similar tolerability to reference trastuzumab in metastatic HER2-positive breast cancer, and similar efficacy and tolerability to reference trastuzumab in women with early HER2-positive breast cancer were proven [69].

Several pharmacokinetic studies were carried out that proved the similarity between PF-05280014 and trastuzumab-EU in terms of pharmacokinetic activity. One of these studies was performed in a multinational, double-blind, randomized, comparative clinical trial testing of PF-05280014 versus trastuzumab-EU, where overall 702 metastatic breast cancer patients were treated with PF-05280014 and trastuzumab-EU. PF-05280014 and trastuzumab-EU had similar pharmacokinetic parameters and influential pharmacokinetic covariates in patients with HER2-positive metastatic breast cancer [72]. Finally, another randomized, double-blind study [71], compared pharmacokinetics, efficacy, safety and immunogenicity of PF-05280014 and trastuzumab reference product as neoadjuvant treatment for operable HER2-positive breast cancer. PF-05280014 demonstrated non-inferior pharmacokinetics and comparable efficacy, safety and immunogenicity to trastuzumab-EU in patients with operable HER2-positive breast cancer receiving neoadjuvant chemotherapy [71].

Further results on safety, efficacy, immunogenicity and overall survival of HER2-positive metastatic breast cancer patients were reported in a randomized, double-blind study comparing PF-05280014 with reference trastuzumab when each patient was given paclitaxel as first-line treatment [73]. The study showed no notable differences between both groups in progression-free survival or overall survival. Safety outcomes and immunogenicity were similar between the treatment groups. Additionally, when given as first-line treatment for HER2-positive metastatic breast cancer, PF-05280014 plus paclitaxel equivalence was demonstrated to trastuzumab-EU plus paclitaxel in terms of objective response rate.

2.2.4 Herzuma (Celltrion)

CT-P6 (Herzuma®) is a trastuzumab biosimilar developed in South Korea by Celltrion. CT-P6 is a HER2 receptor antagonist approved in the European Union for the treatment of HER2-overexpressing breast cancer. It was registered in Brazil by Celltrion with the brand name Herzuma®.

Comparability studies evaluating analytical similarities between CT-P6 and reference trastuzumab demonstrated that it exhibits highly similar structural and physico-chemical properties, as well as ADCC and anti-proliferative activities, compared with the reference trastuzumab [74]. Regarding the glycosylation, galactosylated glycans, sialic acid and glycations, comparison between CT-P6 and the reference products trastuzumab showed that, although significant variabilities were detected in CT-P6, they were in the same range of those observed in the reference product [74].

The clinical comparability between CT-P6 and reference trastuzumab was tested in a randomized, double-blind, two-group, parallel-group, single-dose study to evaluate the pharmacokinetics, safety and immunogenicity of CT-P6 compared to reference trastuzumab in healthy subjects [75]. In this study, equivalence between conditions, with similar serum concentration in the period tested, similar safety profiles, no serious adverse events or deaths, and no subject tested positive for anti-drug antibodies was observed [75].

Further studies included a phase III, double-blind, randomized, parallel group study with active, multicentric, international and prospective control to compare the effectiveness and safety of CT-P6 and reference trastuzumab as neoadjuvant and adjuvant treatment in patients with early-stage breast cancer HER2-positive. This trial demonstrated that neoadjuvant CT-P6 had comparable efficacy to

reference trastuzumab and confirmed the similarity in safety, including comparable risk of cardiotoxicity. When used as adjuvant therapy following neoadjuvant treatment, CT-P6 demonstrated comparability to reference trastuzumab in terms of preventing progressive disease in patients with HER2-positive early-stage breast cancer [76].

Currently, CT-P6 is indicated for the treatment of patients with metastatic breast cancer who have overexpressing tumours with HER2, for the treatment of patients who have already received chemotherapy treatments for their metastatic diseases, in combination with paclitaxel or docetaxel for the treatment of patients who have not yet received chemotherapy. CT-P6 in combination with intravenous capecitabine or 5-fluorouracil (5-FU) and a platinum agent is indicated for the treatment of patients with inoperable, locally advanced, recurrent or metastatic HER2-positive adenocarcinoma of the stomach or gastroesophageal junction, who have not received prior treatment for metastatic cancer [77].

2.3 Infliximab

Infliximab was developed in the United States by Janssen Biotech, approved by the FDA in 1998 and marketed under the brand name Remicade®. It is a chimeric recombinant monoclonal antibody with IgG1 / κ isotype that targets TNF α and was the first TNF α inhibitors used to treat chronic inflammation [78]. It is used for the treatment of several conditions, including inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis and Behçet's disease. There are two infliximab biosimilars approved in Latin America, with broad distribution in the region, marketed under four different brand names in Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Paraguay and Peru (Table 1).

2.3.1 Remsima® /Flixceli® (Celltrion)

CT-P13 (Remsima®/Flixceli®) is an infliximab biosimilar developed in South Korea by Celltrion. It was the first biosimilar monoclonal antibody approved by the European Union [12]. CT-P13 is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis with clinical trials, and by extrapolation for the treatment of psoriatic arthritis and psoriasis. It is also indicated by extrapolation for adults and children older than 6 years for Crohn's disease and ulcerative colitis. In Argentina, CT-P13 was registered by Gobbi-Novag with the brand name Remsima®. In Brazil, Colombia, México and Paraguay CT-P13 was registered by Celltrion as Remsima®. In Chile, CT-P13 was registered by Saval as Remsima®. In Ecuador, CT-P13 was registered by Oxialfarm also as Remsima®. In Peru, CT-P13 is commercialized as Flixceli® and was registered by AC Pharma.

The physicochemical and biological properties of CT-P13 have been extensively characterized compared with those of the reference infliximab, demonstrating high similarity in its physicochemical properties compared to the originator [79]. Among the properties that were evaluated are primary structure and major orders of structure, type, and distribution of glycans, purities/impurities, number and distribution of charged variants, binding to the molecular target and biological potency. A similar activity has also been demonstrated in pharmacodynamics [80], where it has been shown that both have equivalent binding affinities to TNF α , and lack of binding to TNF β and TNF α from other species. *In vitro* studies demonstrated equivalent apoptotic effects and antibody-dependent cell mediated cytotoxicity (ADCC) and CDC, as well as similar cross-reactivity in human tissue [81].

Clinical studies were carried out to demonstrate the equivalence between CT-P13 and reference infliximab in terms of PK/PD, safety and efficacy in patients with rheumatoid arthritis and active ankylosing spondylitis [80, 82]. Furthermore, clinical studies were conducted in patients with ulcerative colitis and Crohn's disease, where comparability with reference infliximab has also been seen in terms of efficacy and safety, thereby also providing evidence of interchangeability between the both [79, 83]. Further evidence of interchangeability has been seen after the change of treatment from reference infliximab to CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis, since it is well tolerated and the results are comparable in terms of efficacy, immunogenicity and safety [80, 82–84].

2.3.2 *Ixifi®/Xilfya®* (Pfizer)

Another infliximab biosimilar is PF-06438179/GP1111 (*Ixifi®* / *Xilfya®*), which was developed in the United States by Pfizer. PF-06438179 was approved by the FDA in 2017 as a treatment for patients with rheumatoid arthritis, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. PF-06438179 was registered in Argentina with the brand name *Ixifi®* by Pfizer. In Brazil, it was registered as *Xilfya®* by Wieth.

Non-clinical comparability studies between PF-06438179 and reference infliximab have shown similar protein structure, with peptide map profiles superimposable and the same peptide masses, indicating identical amino acid sequences. In addition, data on post-translational modifications, biochemical properties, and biological function provided strong support for non-clinical similarity of PF-06438179 [85].

Clinical studies that compared the PK, safety and immunogenicity of PF-06438179 and reference infliximab included a single-dose intravenous administration in healthy adult patients, three-arm, double-blind, randomized (1:1:1) study with parallel groups. The PK results obtained in studies with healthy patients showed similar serum concentrations-time profiles across the treatment groups. Adverse events were similar among PF-06438179 and reference infliximab and the neutralizing and anti-drug antibody profiles were similar between groups [86].

The clinical comparability of PF-06438179 with reference infliximab was tested also in a controlled study in patients with rheumatoid arthritis with an inadequate response to methotrexate. Results show no clinically significant differences in efficacy, pharmacodynamics, immunogenicity and safety among patients receiving PF-06438179 and reference infliximab and in patients who made the transition (single exchange) from reference infliximab to PF-06438179 [87].

2.4 Adalimumab

Developed in the United States by Abbott (today AbbVie), Adalimumab (*Humira®*) was the first fully human monoclonal antibody approved by the FDA in 2002. Adalimumab was approved in 2003 in the European Union with the brand names *Humira®* and *Trudexa®*. It is a fully human IgG1/ κ anti-tumour necrosis factor α (anti-TNF α) monoclonal antibody that prevents the interaction of TNF α with its receptors, thereby interfering with the inflammatory signalling central to chronic autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, paediatric Crohn's disease, moderate to severe chronic psoriasis and juvenile idiopathic arthritis [88]. Currently there are three adalimumab biosimilars approved in Latin America, marketed under three brand names in Argentina, Brazil and Peru (**Table 1**).

2.4.1 Amgevita® (Amgen)

ABP 501 (Amgevita®/ Amjevita®) is a biosimilar of adalimumab developed in the United States by Amgen. It was the first adalimumab biosimilar to be approved by FDA in 2016 and by EMA in 2017 [69]. It is authorized for the treatment of inflammatory diseases in adults, including moderate-to-severe rheumatoid arthritis; psoriatic arthritis; severe active ankylosing spondylitis; severe axial spondyloarthritis; chronic plaque psoriasis; hidradenitis suppurativa; non-infectious intermediate, posterior and panuveitis; Crohn's disease and ulcerative colitis. ABP 501 was registered in Argentina, Brazil and Colombia by Amgen with the brand name Amgevita®. In Peru, ABP 501 was registered by TecnoFarma also with the brand name Amgevita®.

ABP 501 is a fully human recombinant monoclonal antibody with the same amino acid sequence, pharmaceutical form, and dosage strength as reference adalimumab. It is, however, not formulated with the same excipients as adalimumab and includes different buffer components and stabilizers; because of these, several similarity studies between them had been conducted. ABP 501 has been proved to be both analytically and functionally similar to reference adalimumab [89, 90]. Results from analytical studies that evaluated identity, general properties, primary and higher-order structure, carbohydrate structure, isoelectric profile, purity and impurities, and thermal-forced degradation profiles have confirmed ABP 501 to be structurally similar to reference adalimumab [89]. In addition, results from functional characterization studies have demonstrated that ABP 501 and reference adalimumab have similar binding affinity to TNF α and comparable inhibition of TNF α activities *in vitro*. Furthermore, ABP 501 and reference adalimumab have shown comparable induction of effector functions and have also been shown to be similar to adalimumab with respect to binding to a panel of Fc receptors, including Fc γ RIa, Fc γ RIIa, Fc γ RIIIa (158V), Fc γ RIIIa (158F) and FcRn [90].

In terms of pharmacokinetics, a clinical study was conducted in healthy adults who received ABP 501 or reference adalimumab [91]. The results of the study showed that there were no meaningful differences between ABP 501 and reference adalimumab in terms of safety, efficacy and immunogenicity under the conditions of use approved for adalimumab and in accordance with the regulations and guidance for biosimilars development [91]. Phase III clinical studies have shown that ABP 501 and reference adalimumab have similar clinical efficacy, safety and immunogenicity profiles over 52 weeks of treatment in a sensitive population of immunocompetent patients with psoriasis [92]. Additionally, data from a different randomised, double-blind, phase III equivalence study in patients with moderate-to-severe rheumatoid arthritis has indicated that the clinical efficacy, safety and immunogenicity of ABP 501 is similar to that of reference adalimumab [93].

2.4.2 Hyrimoz® (Sandoz)

The adalimumab biosimilar GP2017 (Hyrimoz®) was developed in Germany by Sandoz and in 2018 was authorized in the European Union for use in patients with rheumatoid arthritis, plaque psoriasis, Crohn's disease, uveitis and ulcerative colitis and all indications for which reference adalimumab is approved [94]. GP2017 was registered in Brazil by Sandoz with the brand name Hyrimoz®.

GP2017 has been shown to exhibit similarity to reference adalimumab with respect to primary, secondary, and tertiary structures, carbohydrate structure, molecular size, charges, and impurities. Differences between GP2017 and reference adalimumab in glycosylation variants were not clinically relevant [94]. Similarity was also determined in functional activity determinations of binding to TNF α , to the human Fc γ receptor subtypes, and to FcRn. Other functional comparative

studies include CDC, ADCC, C1q, apoptosis inhibition and apoptosis induction/reverse signalling [95].

A comparability clinical study of GP2017 with reference adalimumab was performed to evaluate similarity in pharmacokinetics, safety and immunogenicity over 72 days post injection [96]. In the study, maximum serum concentration and AUC from the time of dosing extrapolated to infinity were observed within the predetermined margin of similarity between GP2017 and reference adalimumab. Most treatment emergent adverse events were mild or moderate in intensity and the determination of anti-drug antibodies was similar between groups, with 57.9% GP2017, 69.8% for EU-adalimumab and 69.5% for US-adalimumab [96].

In addition, the clinical efficacy of GP2017 compared to that of reference adalimumab was tested in a phase III randomized study in psoriasis in patients with moderate-to-severe plaque psoriasis or rheumatoid arthritis. In this study, it was shown that the tolerability, safety and immunogenicity profiles of the two agents were similar. The efficacy between groups was shown, where multiple switching between GP2017 and reference adalimumab (up to four times) had no impact on efficacy, tolerability, or immunogenicity. The role of reference adalimumab in the management of autoimmune inflammatory conditions is well established and this study provides evidence that GP2017 is an effective biosimilar alternative for patients requiring adalimumab therapy [97].

2.4.3 Xilbrilada® (Pfizer)

PF-06410293 (Abrilada®/Xilbrilada®) is a biosimilar of adalimumab developed in the United States by Pfizer and approved by the FDA in 2019, where it is marketed with the brand name Abrilada®. PF-06410293 is indicated for the treatment of patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis and juvenile idiopathic arthritis. PF-06410293 was registered in Brazil by Wyeth, where it is marketed as Xilbrilada®.

Comparative non-clinical studies between PF-06410293 and reference adalimumab were conducted and they confirmed similarity [98]. Structural analysis evaluating peptide mapping showed similar chromatographic profiles, confirming that the amino acid sequences PF-06410293 and reference adalimumab are identical. Data on post-translational modifications, biochemical properties, and biological function provided strong support for analytical similarity. Binding to TNF α was similar for PF-06410293 and reference adalimumab. In addition, *in vivo* studies in rats showed that intravenous application of PF-06410293 and reference adalimumab were well tolerated, and exhibited similar pharmacokinetics, with equivalent maximum drug concentration and AUC [98].

The clinical similarity between PF-06410293 and reference adalimumab was tested in a clinical study, double-blind, randomized, comparative, efficacy of individuals with severely active rheumatoid arthritis and with inadequate response to methotrexate. The study demonstrated therapeutic equivalence (similarity) and similar responses between treatments with PF-06410293 and reference adalimumab. The study shows the absence of clinically significant differences in efficacy, pharmacodynamics, immunogenicity and safety between individuals who received PF-06410293 or reference adalimumab. Moreover, equivalent response was observed in patients who transitioned from PF-06410293 to reference adalimumab, and those who transitioned from reference adalimumab to PF-06410293. The comparative results obtained in this study in individuals with rheumatoid arthritis on background methotrexate provide further evidence of high similarity between reference adalimumab and PF-06410293 [99].

2.5 Bevacizumab

Bevacizumab (Avastin®) is a humanized monoclonal antibody with IgG1 / κ isotype that targets the vascular-endothelial growth factor (VEGF), which in turn prevents endothelial proliferation and inhibits angiogenesis. It was developed by Genentech, receiving its first approval in the United States in 2004 by the FDA, and currently is marketed by Roche. Originally indicated in combination use with standard chemotherapy against metastatic colon cancer, it has since been approved for use in certain lung cancers, renal cancers, ovarian cancers and glioblastoma multiforme of the brain. Two biosimilars of bevacizumab are commercialized in Latin America by 2021. They are approved in Argentina, Brazil, Colombia, Ecuador and Paraguay, and traded under two brand names (**Table 1**).

2.5.1 Bevax® (*mAbxience*)

BEVZ92 (Bevax®) is an antibody biosimilar of bevacizumab developed in Argentina by PharmaADN (today mAbxience) and marketed by Laboratorios Elea in Argentina. It is indicated in combination with other chemotherapy and biologic agents for metastatic cancer from colon [100], and by extrapolation to adults with metastatic cancer from rectum, breast, kidney, glioblastoma, ovary, peritoneum, uterus, and non-small cell lung cancer. BEVZ92 is distributed by Grünenthal in Ecuador and distributed by Laoratorios Bioéticos in Paraguay with the brand name Bevax®.

The clinical comparability of BEVZ92 and reference bevacizumab was performed in the clinical trial NCT02069704, which was completed in June 2017. This was a multi-centre, open-label, bioequivalence study of BEVZ92 and reference bevacizumab, randomized with 2 parallel arms to compare efficacy, safety, immunogenicity and the pharmacokinetic profile of BEVZ92 and reference bevacizumab in combination with chemotherapy for metastatic colorectal cancer [100]. Patients have shown similarity in pharmacokinetics comparing the geometric mean ratio of AUC in patients treated with BEVZ92 and with reference bevacizumab [100]. In addition, the objective response, clinical benefit and progression-free survival were similar for BEVZ92 and reference bevacizumab groups. The safety profile did not show relevant differences between both study arms, with similar levels of grade 3 or 4 adverse events and serious adverse [100]. The immunogenicity assessed as the incidence of anti-drug antibodies was similar and low for both study arms. The reported results show that, when used in the same way, BEVZ92 and reference bevacizumab are highly similar in terms of PK, immunogenicity, safety and efficacy for the treatment of metastatic colorectal cancer. Romera et al. also reported that BEVZ92 was similar to reference bevacizumab in an extensive physicochemical and functional characterization, including primary structure, higher order structure, biological activity, and binding affinity to VEGF, although the data was not shown [100].

In 2016 a Treatment Registry for the pharmacovigilance of BEVZ92 was established to collect adverse drug reactions (ADRs) from patients treated with this biosimilar. Physicians have sent information to this registry from 818 patients treated with BEVZ92 between 2016 and 2018 for metastatic colorectal cancer, epithelial ovarian cancer, recurrent, metastatic or persistent cervical cancer, metastatic breast cancer, advanced non-small cell lung cancer, glioblastoma, advanced or metastatic renal cell carcinoma, and off-label clinical cancer indications [101]. Of those, 416 patients that had at least one follow-up point were included for analysis, with 44 reports filed involving 51 ADRs (23 serious). The comparison of the list of ADRs in cancer patients for BEVZ92 with those for reference bevacizumab in post-marketing surveillance studies show similarity to the reference antibody, but the relative low

number of reports emphasize the need to continue with this pharmacovigilance program to better establish the safety profile of BEVZ92 in cancer patients [101].

2.5.2 *Mvasi*® (*Amgen*)

ABP 215 (*Mvasi*®) is a bevacizumab biosimilar developed by Amgen in the US. It was the first biosimilar of this originator monoclonal antibody to be approved by the FDA in 2017 and by the EMA in 2018 [69]. ABP 215 is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer and epithelial ovarian, fallopian tube, primary peritoneal or cervix cancer. ABP 215 is commercialized by Amgen in Argentina, Brazil and Colombia with the brand name *Mvasi*®.

Analytical tests to evaluate the similarity between ABP 215 and originator bevacizumab demonstrated that both products have the same peptide sequence, and that the glycosylation profile was similar. The biological and functional activities of ABP 215 and reference bevacizumab shown similar binding and inhibition of VEGFR-2 signalling among groups. More than 20 batches of original bevacizumab and 13 batches of ABP 215 were assessed for similarity and showed that structural and purity attributes, and biological properties are highly similar between them [102].

To assess the pharmacokinetics, safety, tolerability and immunogenicity equivalence of the biosimilar ABP 215 and reference bevacizumab, a randomized, single-blind, single-dose, phase I clinical study was performed. In this trial, the maximum observed serum concentration and AUC was similar between ABP 215 and reference bevacizumab. Furthermore, the safety profiles showed no difference, with no deaths or adverse events leading to study discontinuation, and no subject was positive for binding anti-drug antibodies [61].

The clinical equivalence in terms of safety, immunogenicity and efficacy between ABP 215 and original bevacizumab was evaluated in a phase III clinical trial in patients with advanced non-squamous non-small cell lung cancer. The frequency, type, and severity of adverse events were comparable between ABP 215 and reference bevacizumab, and no patient tested positive for anti-drug neutralizing antibodies. Moreover, the clinical efficacy of ABP 215 and reference bevacizumab was similar, with 39.0 and 41.7% patient overall response respectively. The data in this clinical trial supports a clinical equivalence ABP 215 and original bevacizumab [103].

3. Conclusion

In the last decade, progress made in the regulatory pathways to register biologic medicines with very high-quality standards allowed the approval of the first generation of biosimilar monoclonal antibodies in Latin America that showed robust evidence of safety and efficacy. This process occurred in parallel with the expiration of the patents of the earlier therapeutic monoclonal antibodies. By the end of 2021, biosimilar antibodies of rituximab, trastuzumab, infliximab, adalimumab and bevacizumab are expected to be commercialized in the region with 25 different brand names. This trend is stronger in countries like Brazil and Argentina, which have more than ten different biosimilar monoclonal antibodies approved and, as is the case for trastuzumab, three different biosimilars approved competing with *Herceptin*®, the antibody of reference. It is expected that more approvals of highly controlled biosimilars will increase the market competition and result in a significant reduction of prices compared to the reference monoclonal antibodies, without a compromise in quality and safety.

Acknowledgements

FONCYT-IP-COVID 19 N° 929, FONCYT- PICT2018-3954, Fundación Bunge y Born, INC 2018-2020, PID 2015-0034, Fundación Williams, and Fundación René Barón funded G.H., who is a member of Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). P.K., M.G. and S.F. were funded by CONICET Doctoral Fellowships. Varifarma S.A. has partially funded the Grant PID 2015-0034 directed by Dr. Gustavo Helguera.

Conflict of interests


Varifarma S.A. has partially funded the Grant PID 2015-0034 directed by Dr. Gustavo Helguera.

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*Edited by Valderilio Feijó Azevedo
and Robert Moots*

Introduced in the 1980s, biologic medications have since become important tools in modern medicine. However, biologics are expensive, greatly affecting the healthcare budgets of both underdeveloped and developed countries. Fortunately, biosimilars, which are highly similar, reverse-engineered versions of existing biological medicines and their active ingredients, are now available as more affordable options for patients treated with biologics. This book discusses biosimilars with chapters on clinical trials, regulation, pharmacovigilance, and the interchangeability of biosimilars with biologics. It also addresses future trends in the biosimilars market.

Published in London, UK

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