

New monoclonal antibody biosimilars approved in 2015 in Latin America: position statement of the Latin American Forum on Biosimilars on biosimilarity, interchangeability and extrapolation of indications

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Introduction: The Latin American Forum on Biosimilars (FLAB) is an annual meeting that brings together various stakeholders, including key opinion leaders, the pharmaceutical industry, academics, patients, lawyers and other healthcare professionals, to present and discuss recent findings regarding biosimilars. In 2015, the meeting theme was interchangeability and automatic substitution. Regarding biosimilarity, interchangeability and extrapolation of indications, the discussion centred on two products in Brazil and Argentina: CT-P13, an infliximab biosimilar; and RTX83, a rituximab biosimilar. Here, we conduct a critical analysis of the available scientific and medical information on these products to establish a FLAB position statement in the context of the current regulations in Brazil and Argentina.

Biosimilarity, interchangeability and extrapolation of indications: RTX83 is still not approved in Brazil and is currently under a technology transfer agreement. In Argentina, the drug was approved for commercialization under the name Novex, with extrapolation of indications for rheumatoid arthritis, which according to the Argentinian Society of Rheumatology, lacks the necessary clinical data for such an approval. CT-P13 is already approved in Brazil, and is on the market. The approval was based on the data presented in the PLANETAS and PLANETRA studies. Interchangeability will not be considered for this product until further studies are presented.

Discussion: Based on the available evidence, CT-P13 is the only biological molecule marketed in Latin America that can be considered a true biosimilar. Extrapolation is only acceptable when the diseases for which the reference product is intended to treat are entirely similar. Extrapolation based on only preclinical studies is not acceptable. Conversely, although the proposed rituximab biosimilar (RTX83) was approved by ANMAT (National Administration for Medicines, Food and Medical Technology) in Argentina, clinical data demonstrating its equivalence with the reference rituximab, is necessary before RTX83 can be considered a true biosimilar.

Keywords: Biosimilarity, extrapolation, infliximab, interchangeability, monoclonal antibodies, rituximab

Introduction

The annual Latin American Forum on Biosimilars (FLAB) was first held in 2010 with the aim of bringing key stakeholders within the community together to discuss aspects of biosimilars. Attended by key opinion leaders, representatives from

the pharmaceutical industry, academics, patients, lawyers and healthcare professionals, FLAB is sponsored or supported by different organizations, including the pharmaceutical industry such as AbbVie, Janssen, Pfizer, Sandoz, Sanofi; patient organizations and Latin American medical

societies such as Brazilian Society of Rheumatology, Argentinian Society of Rheumatology, GEDIB (Brazilian Study Group of Inflammatory Bowel Diseases) among others; some regulatory agencies such as ANVISA (*Agencia Nacional de Vigilancia Sanitaria*), COFEPRIS (*Comisión Federal para la Protección contra Riesgos Sanitarios*), ANAMED (*Agencia Nacional de Medicamentos*), have sent representatives to the Forum in order to discuss regulatory aspects of biosimilars approved in their countries. The 2015 meeting was held in Brasília, Brazil, with the theme of 'Interchangeability and Automatic Substitution', and saw the approval of two potential biosimilars in different Latin American countries.

The World Health Organization (WHO) defines similar biotherapeutic products (SBPs) as products that are similar in terms of quality, safety and efficacy to an already-licensed reference biotherapeutic product (RBP) [1]. An SBP is tested for biosimilarity via a biosimilarity exercise in which it is compared with existing products using the same procedures. Within this biosimilarity exercise, there are three levels of evaluation: quality evaluation (i.e. physicochemical and biological characterization), non-clinical evaluation and clinical evaluation. Clinical evaluation seeks to demonstrate the comparable safety and efficacy of the SBP with the RBP. It is a stepwise procedure that begins with pharmacokinetic (PK) and pharmacodynamic (PD) studies, followed by efficacy and safety clinical trial(s). Given that biotherapeutic products are biologically active molecules capable of inducing immune responses, immunogenicity is an important consideration within the evaluation of safety. In our opinion, all biological products supported by a full biosimilarity exercise can be considered true biosimilars. Conversely, products that are not fully supported by scientific information, including comparative clinical data, cannot be considered biosimilars.

In Europe, a similar definition has been established that states: 'biosimilars are copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biological products' [2]. This conceptual idea has been well established by the European Medicines Agency's (EMA) guidelines [3], which have led to the approval of several biosimilars in Europe, including the first biosimilar monoclonal antibody (mAb), the

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anti-tumour necrosis factor (anti-TNF) drug infliximab. In September 2013, the Committee for Medicinal Products for Human Use (CHMP) of EMA, approved the use of biosimilar of Remicade™ under the trade names of Remsima™ and Inflectra™ [4, 5].

Other biosimilar mAbs and fusion proteins that are currently being investigated include: rituximab, which is in the early stages of clinical trials; and adalimumab and etanercept, which are in phase III clinical trials.

The main objective of this paper is to provide a critical analysis of the results of the biosimilarity exercises carried out on two products that have been recently approved in Brazil and Argentina: CT-P13, an infliximab biosimilar; and RTX83, a proposed rituximab biosimilar. As a result, we have established a FLAB position statement on the approval of these drugs in the context of the current regulations in Brazil and Argentina.

Biosimilarity, interchangeability and extrapolation of indications: the case of CT-P13 and RTX83 in Brazil and Argentina

At present, a number of countries in Latin America have specific regulations concerning the approval of SBPs (Argentina, Brazil, Chile, Costa Rica, Cuba, Guatemala, Mexico, Panama, Peru and Venezuela). In general, regulations consider the international standards set out by EMA, in combination with local input and scientific principles based on WHO guidelines. Most legislation for biosimilar approval considers it essential to implement a system of pharmacovigilance after product commercialization, to ensure that the safety and efficacy of biosimilars can be evaluated [6].

In Argentina, resolutions outlining the requirements for biopharmaceuticals and biosimilar products (No. 7075 [7] and 7729 [8]) were published in 2011 by the ANMAT. Resolution No. 7729 specifically states the requirements for the approval of biosimilars. Of note, Article 6 states that the comparative exercise between the reference product and proposed biosimilar must be accompanied by non-clinical and clinical studies in order to be approved. In 2012, ANMAT enacted Resolution No. 3397, which established the requirements for the approval of biological medicines obtained using DNA recombinant technology, including mAbs [9].

In 2013, the Brazil-based pharmaceutical company, Libbs, and the Chemo Group's

biotechnology company, mAbxience, signed a licensing and technology transfer agreement for several biosimilar mAbs developed by mAbxience, including the rituximab biosimilar. A clinical trial sponsored by mAbxience entitled: 'A Randomized, Double-blind, Phase III Study Comparing Biosimilar Rituximab (RTXM83) Plus CHOP Chemotherapy Versus a Reference Rituximab Plus CHOP (R-CHOP) in Patients With Diffuse Large B-cell Lymphoma (DLBCL) Given as First Line' was registered under the ClinicalTrials.gov identifier NCT02268045 on 19 September 2014. Libbs and Elea, an Argentina-based company, are among the collaborators that worked towards establishing this protocol. This study is a non-inferiority trial and is currently recruiting participants. Despite this, in Argentina, ANMAT enacted Regulation No. 7060 (dated 2 October 2014), which authorized the commercialization of the biopharmaceutical product Novex (sponsored by Elea), that contains the rituximab biosimilar, RTX83 [10]. As clinical trials are ongoing, it is evident that this was approved by ANMAT without any clinical data which is contrary to legislation [7-9].

Novex is now being distributed in hospitals and health centres in Argentina to be administered to patients diagnosed with rheumatoid arthritis (RA). As this product has been approved without clinical data, the Argentine Society of Rheumatology has issued a statement suggesting their associates do not administer Novex to patients.

In contrast, a very different situation exists in Brazil. The infliximab biosimilar, CT-P13 (Remsima™), sponsored by Celltrion, received market approval by ANVISA in 29 April 2016. This approval was based on full clinical development, including a phase I clinical trial, known as the PLANETAS trial [11], which compared treatment with CT-P13 to innovator infliximab in individuals with active ankylosing spondylitis. The outcomes, pharmacokinetics and clinical efficacy, including the Assessment in Ankylosing Spondylitis Response Criteria (ASAS) 20 and ASAS 40 responses, were similar in both treatment groups; and the product safety profiles were also comparable up to week 30. After this, a phase III clinical trial, known as the PLANETRA trial [12], was performed, which compared CT-P13 to innovator infliximab in patients with active RA who did not respond well to methotrexate treatment. Equivalence was demonstrated in the American College of Rheumatology 20% (ACR 20) response

at week 30. Currently, several trials with proposed biosimilars are in progress and it seems highly likely that approval and marketing of new products will be requested in the near future [13].

Discussion

Evidence suggests that, although the infliximab biosimilar, CT-P13, was approved in Brazil following full development that demonstrated clinical biosimilarity, interchangeability with the infliximab innovator is not guaranteed. Biosimilars cannot be considered interchangeable or a substitute for their reference product based solely on biosimilarity evidence. It should be left to the clinician's judgement to choose whether to switch from an originator to a biosimilar. Other paramedical individuals and healthcare payers should not be allowed to change prescriptions or impose the use of biosimilars instead of their originator. Biosimilars should be considered interchangeable if the manufacturer has demonstrated that the drug can produce similar effects to the reference product in any given patient. Moreover, Brazilian medical societies point out that when a biological product is administered to an individual more than once, the risk, in terms of safety or diminished efficacy, of alternating between using the biosimilars and the reference product, is not greater than the risk of using the reference product without such alteration or switch [12]. The best approach should be to conduct a rigorous clinical study to evaluate the possibility of the reference and biosimilar being interchangeable.

The NOR-SWITCH trial (NCT02148640) [14] is a prospective randomized study that aims to examine the ease with which CT-P13 can be interchanged with the infliximab innovator. The authors plan to recruit 500 patients with five different indications for infliximab: RA, plaque psoriasis, ankylosing spondylitis (AS), Crohn's disease (CD) and ulcerative colitis (UC). All patients will be treated with the infliximab innovator for six months. After this time, half will switch to treatment with CT-P13 and the other half will remain on the infliximab innovator. After 52 weeks, clinical observations will be made by physicians and patients to determine the efficacy of the switch. It is hoped that this will provide robust evidence in support of switching from the reference product to the biosimilar. However, it is generally accepted that clinical trials to assess interchangeability should have crossover or Balaam's design [15], neither of

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which are incorporated in this trial; therefore, it cannot be considered an appropriate interchangeability study. No biosimilar should be considered interchangeable until proven by clinical medical evidence [16].

An example of such an interchangeability trial was recently carried out in Italy. Data from the Prospective Observational Cohort Study on patients with inflammatory bowel disease receiving Therapy with BIOsimilars (PROSIT-BIO), obtained from patients with UC and CD, was presented at the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD), VII National Congress in Palermo [17]. With 397 patients (174 UC and 223 CD), this is the largest interchangeability study carried out to date. It demonstrated that comparable efficacy was observed in patients who were switched from the infliximab innovator to the infliximab biosimilar (93 patients), compared to patients receiving a biosimilar who had previously been naïve to anti-TNF (217 patients), and patients receiving a biosimilar who had previously been exposed to one or more biologicals (87 patients) (response rate 95% vs 92% vs 91%, respectively). Safety was also found to be comparable across the patient groups.

Extrapolation of indications is a regulatory decision. CT-P13 is an example of this because it was extrapolated in more than 50 countries including Brazil. This decision is controversial because the biosimilarity of CT-P13 was tested in only two disease models, RA and AS, and then extrapolated to inflammatory bowel disease. The Brazilian regulation of biosimilars, such as RDC 55/2010, has two pathways: individual and comparability. When a biosimilar is only submitted to the individual pathway, it is not possible to extrapolate indications. Submissions must also be made to the comparability pathway in order to enable the extrapolation of indications.

Conversely, Argentinian regulation of biosimilars does not permit extrapolation of indications. The case of the rituximab biosimilar RTX83, which was approved in Argentina, is challenging. To the best of our knowledge, this product has been approved for all the indications of the rituximab innovator without any clinical data. Therefore, this product is not a true biosimilar because biosimilarity, with respect to the reference product, has not been fully demonstrated.

Statement

Based on the evidence, CT-P13 is the only monoclonal antibody marketed in Latin

America that can be considered a true biosimilar. Extrapolation is only acceptable when the diseases for which the reference product is used to treat are entirely similar. Extrapolation based on only preclinical studies is unacceptable. Currently, there is no clinical evidence to support that CT-P13 and the reference product are interchangeable.

Conversely, although the proposed rituximab biosimilar (RTXM83) was approved by ANMAT in Argentina, clinical data demonstrating its equivalence with the reference rituximab is necessary before RTX83 can be considered a true biosimilar.

The interest in biosimilars is growing in Latin America due to a number of factors, including the large proportion of healthcare resources that are used to import high cost branded biologicals. Biosimilars are expected to reduce drug expenditure, assuming that they achieve similar clinical results as the reference product. The need for well-defined pathways and regulations for the review, approval and pharmacovigilance of biosimilars, as well as greater transparency of the actions of governments, are required to facilitate appropriate biosimilar approval and usage. As both Brazil and Argentina have specific regulations concerning the approval of biosimilars, their governments are responsible for guaranteeing the approval of safe and effective biosimilar products.

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Visit the link www.biossimilares2016.com.br for further information on FLAB.

Competing interests: Adjunct Professor Valderílio Feijó Azevedo is a speaker for AbbVie, AstraZeneca, BMS, Celltrion, Janssen, Novartis, Pfizer, Roche, Sanofi, UCB; and has produced graphic material to AbbVie, Janssen, BMS, Pfizer. He is also a member of the advisory board of AbbVie, AstraZeneca, BMS, Janssen, Merck Serono, Pfizer. Alejandra Babini declares that she is President of the Argentinian Rheumatology Society. She is a consultant, speaker and member of the advisory board of AbbVie and Pfizer. Fabio Vieira Teixeira declares that he is a consultant, speaker and a member of the advisory board of Janssen and Hospira/Pfizer. He is also a consultant and speaker of Ferring and Nestlé. Igor Age Kos and Pablo Matar declare no relevant conflict of interests to participate in this authorship.

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