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Practical Guidance on Biosimilars, With a Focus on Latin America

What Do Rheumatologists Need to Know?

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Background/Historical Perspective: Availability of biologic disease-modifying antirheumatic drugs (bDMARDs) has improved clinical outcomes in rheumatoid arthritis, but it also increased the cost of treatment. Biosimilars, the regulated copies of biologic products, have a potential to reduce health care costs and expand access to treatment. However, because of a complex development process, biosimilars can be considered only those noninnovator biologics with satisfactory supporting evidence (ranging from structural to clinical), as outlined in the recommendations by the World Health Organization (WHO). In Latin America, a heterogeneous regulatory landscape and nonconsistent approval practices for biosimilars create decision-making challenges for practicing rheumatologists.

Summary of Literature: Most Latin American countries either have adopted or are in the process of adopting guidelines for the approval of biosimilars. However, among several marketed bDMARDs in the region, currently there are only 2 products that could be considered true biosimilars, based on the WHO criteria. The rest can be considered only intended copies, whose safety and efficacy are not fully established. One such product had to be withdrawn from the market because of safety concerns.

Conclusions and Future Directions: Practicing rheumatologists in Latin America need to understand the regulatory situation for biosimilars in their countries. When considering bDMARDs that are not innovator products, clinicians should use only those that have been approved according to the WHO recommendations. For clarification, local health authorities or professional associations should be contacted.

Key Words: biologic, biosimilar, intended copy, regulatory

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The discovery of the role of tumor necrosis factor α (TNF-α) in the pathogenesis of rheumatoid arthritis (RA) and the advances in recombinant DNA technology heralded a new era of targeted therapeutics for this condition. The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs), comprising monoclonal antibodies and fusion proteins that target TNF-α, as well as other mediators of the inflammatory response, has significantly expanded the treatment options for patients with RA over the past 2 decades.[1]

The effectiveness of bDMARDs resulted in their widespread use, but it also contributed to escalating health care spending,[1,2] which in turn focused attention on possible cost control options, including the manufacture process and reimbursement practices.[3] Patent expiration of an innovator biologic drug also creates an opportunity for developing "similar biotherapeutic products,"[4] also known as biosimilars.[5]

With the increasing availability of biosimilars, disparities between countries in terms of the regulatory pathways and the quality of the evidence required to achieve market authorization have become clear. Not all countries adhere to the recommendations of World Health Organization (WHO)[4] or follow regulatory approval practices similar to those of the US Food and Drug Administration (FDA)[6] or the European Medicines Agency (EMA).[7] As a result, potential biosimilars may differ in their structure or physicochemical properties from the innovator products to such an extent that they cannot be considered biosimilars and are therefore termed "noncomparable biotherapeutic products,"[8] "biomimics,"[9] or "intended copies."[10] (In this article, the term "intended copies" will be used.)

The risk of making biologic products available without a proper evaluation of their clinical characteristics can be illustrated by the example of Kikuzubam, an intended copy of rituximab. This product was widely marketed in Mexico,[11] without publicly available clinical data to support an assessment of biosimilarity with the innovator molecule, only to be withdrawn by the Mexican Federal Commission for Protection Against Health Risks in 2014 because of safety concerns.[9]

Therefore, clinicians may face serious challenges when considering a biologic treatment option for their patients. This article draws on the perspectives of a group of Latin American rheumatologists and pharmacologists and aims to provide key information to support clinicians in making informed decisions about the use of biosimilars in the treatment of rheumatic diseases.

Framework for the Approval of Biosimilars

The manufacturing of biosimilars is inherently associated with variability, leading to some level of heterogeneity between batches.[12] Therefore, the development of biosimilars creates a challenge—usually not encountered with the generic versions of small molecules—of accumulating knowledge and experience related to the process and product characterization.[13] Specific details of cell line development, genetic construct, raw materials used, cell culture conditions, purification parameters, formulation,

and drug delivery are usually proprietary and therefore not available to the prospective manufacturers of biosimilars, which creates a knowledge gap.[14] This gap is central to explaining the difference in the regulatory requirements between comparability (e.g., comparing batches of the same licensed biologic product, made by the same manufacturer, after a change in the manufacturing process) and biosimilarity (extensive assessment of a biologic produced by a different manufacturer in order to demonstrate a high degree of similarity to the originator) (Fig. 1). For all these reasons, biosimilars cannot be considered generics of biologic therapies.

In order to establish biosimilarity to the innovator product, various regulatory agencies adhere to the "totality of evidence" approach, in which a wide range of information is submitted with the application, including the reports on structural and functional characterization, nonclinical evaluation, human pharmacokinetic (PK) and pharmacodynamic (PD) studies, clinical immunogenicity assessments, and comparative clinical data versus the reference product.[6]

The WHO recommends that the application for a biosimilar demonstrate an absence of clinically meaningful differences with respect to the reference product.[4] The WHO recommendations are reflected in the regulatory guidelines for biosimilars issued by the FDA[6] and the EMA.[17] Although these guidelines do differ in some minor aspects,[18] they both require a stepwise approach, based on structural, functional, pharmacologic, and clinical similarities. Both sets of guidelines allow for the possibility of requesting comparative clinical studies with the reference product, but note that such studies may not always be necessary.[19] However, the WHO standards for approval of biosimilars,[4] including the WHO-recommended steps for regulatory risk assessment,[20] have not been adopted by all regulatory agencies.

Regulatory Pathways to Biosimilarity: A Snapshot of Latin America

The majority of Latin American countries are in the process of establishing their own standards for regulating biosimilars,[21] and the regional recommendations on how to ensure the safety and effectiveness of biosimilars are available.[22] Despite the existing framework, national guidelines on interchangeability and naming are still lacking, and the pharmacovigilance systems are very bureaucratic and feel remote from clinical practice for many physicians. The general features of that regulatory landscape have been reviewed recently[23] and are illustrated in Figure 2.

In Argentina, the national Administration of Drugs, Foods and Medical Devices (ANMAT) introduced a formal regulatory pathway in 2011 and has been instrumental in establishing the need for rigorous approval standards in the region.[24] Nevertheless, ANMAT authorized the commercialization of the rituximab biosimilar RTXM83 (under the trade name of Novex) prior to the completion of required clinical trials, which was in violation of their own regulations.[25] In response, the Argentine Society for Rheumatology suggested its members not to use Novex in their clinical practice. Similarly, the agency approved Novex for the treatment of lymphoma and extrapolated its approval to all other indications authorized for the innovator product, again without availability of phase 3 trial data.[26]

Brazil is unusual in having 2 regulatory pathways, "comparative" and "individual," introduced by the National Health Surveillance Agency in 2010.[27] The comparative pathway is based on the WHO recommendations, and products licensed via this route are considered to be biosimilars.[28] The anti-RA bDMARDs licensed using the "comparative" pathway include Remsima, a biosimilar of infliximab, approved in 2015,[29] and Brenzys (SB4), a biosimilar of etanercept, approved in 2017.[30] The individual pathway does not require comparisons with the innovator product, but the manufacturer is not allowed to apply for extrapolation of therapeutic indications. Therefore, the agents approved using this pathway cannot be considered biosimilars but intended copies only.

The ANAMED, national drug agency of Chile, has yet to release its biosimilars guidelines, but a draft issued in 2011 suggests Chilean regulators will draw upon the EMA and WHO documents.[31]

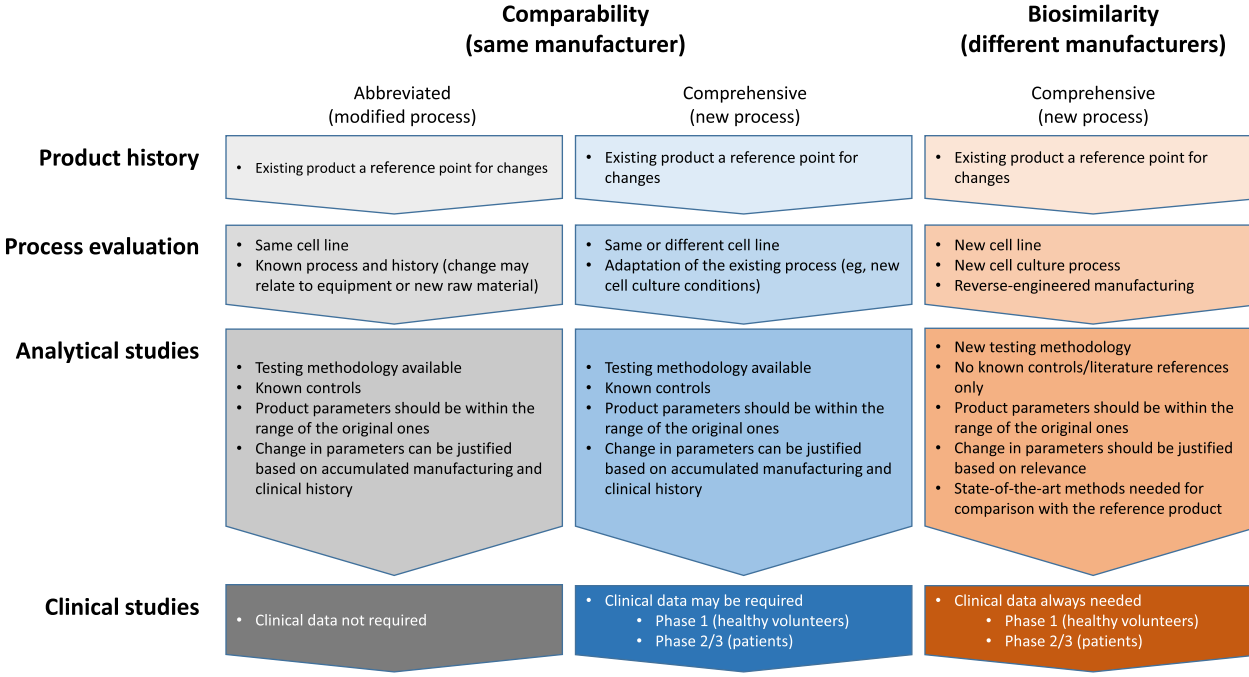

FIGURE 1. Requirements for comparability and biosimilarity exercises (adapted from Azevedo et al[15] and Declerck et al[16]) Color online-figure is available at http://www.jclinrheum.com.

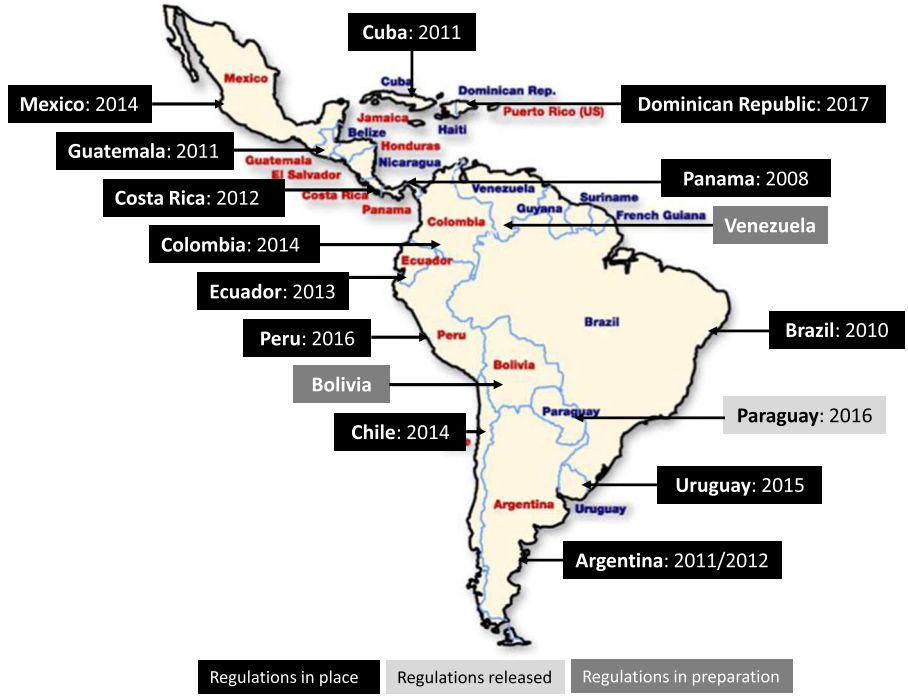

FIGURE 2. The regulatory landscape for biosimilars in Latin America (adapted from Garcia and Araujo[23]). Regulatory/legislative citations: Argentina—Disposición 7729/2011 for biosimilar drugs and Disposición 3397/2012 for biologic products; Brazil—RDC 55/2010; Chile—NORMA 170, 2014; Colombia—Decree 1782 of 2014; Costa Rica—Reglamento Tecnico RTCR 440 2010; Cuba—Regulación no. 56/2011; Ecuador—Reglamento para la Obtencion del Registro Sanitario, Control y Vigilancia de Medicamentos Biológicos para Uso y Consumo Humano, issued on May 17, 2013 (Chapter VII); Formulario de requisites que se deben adjuntar para el registro sanitario de medicamentos biológicos extranjeros en general y por homologación (August 8, 2013); Guatemala—Ley 4245; Mexico—NOM 257 and NOM 177; Panama—Decreto Ejecutivo no. 32, February 11, 2008; Paraguay—Decreto no. 66/1, December 12, 2016; Peru—Decreto Supremo no. 011-2016-SA and no. 013-2016-SA; Uruguay—Decreto no. 38/015. Color online-figure is available at http://www.jclinrheum.com.

In January 2013, The Colombian Ministry of Health and Social Protection released a new draft guideline for biologics, including similar biotherapeutic products,[32] which allows for 3 different routes of approval: (1) a complete application for new biologics, (2) a comparability route for products that are not new but require additional characterization, and (3) a short route for well-known, fully characterized products. The plan also calls for establishing a risk management plan (RMP) and requires assessment of immunogenicity issues.[33] In December 2014, INVIMA, the Colombian food and drug administration agency, approved Remsima as its first "similar biotherapeutic product."[32] Previously, the agency had authorized the use of Etanar, an intended copy of etanercept, via the approval pathway normally used for small-molecule generic drugs.[10]

In 2009, The Cuban Center for State Control of the Quality of Drugs (CECMED) issued a position paper[34] establishing the basic principles for regulation of biosimilars, which are somewhat different from those recommended by the WHO, and a set of requirements for the registration of biologic products was released in 2011.[35] To date, however, CECMED has not approved any bDMARD for rheumatic diseases (rituximab is used for non-Hodgkin lymphoma only).[36]

Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) issued its guidelines for "biocomparable medicines" in April 2012, at the time when numerous noninnovator biologics were already on the market.[37] This includes the aforementioned Kikuzubam, an intended copy of rituximab that was withdrawn from the market because of safety concerns, and Infinitam, an intended copy of etanercept, whose registration was set to expire in October 2017, after the 5-year authorization period. (It remains to be seen whether COFEPRIS will request a full dossier, including clinical data, for reauthorization of Infinitam.) COFEPRIS also issued rules for noninnovator biologicals registered prior to October 19, 2011 (when the guidelines for biocomparable medicines were first published), mandating that companies marketing these products conduct clinical trials to establish biosimilarity and submit their data to the commission.[37] The Mexican College of Rheumatology also published a position paper on biosimilars regulation,[38] voicing their support for biosimilars development, provided they are subject to the highest standards of production and development, including adequate clinical studies, and followed by a strict pharmacovigilance program. The infliximab biosimilar Remsima was the first biocomparable medicine approved following the full procedure required by the COFEPRIS,[39] and the manufacturers of future biosimilars will likely be required to follow this path.

In addition to national initiatives, region-wide efforts are also taking place. For example, in order to assist policy makers in Latin American countries, a group of experts considered the major issues related to establishing an effective pharmacovigilance system and provided recommendations for its implementation.[22] The group proposed an RMP, to be developed by the manufacturer, with the goal to identify, characterize, and manage the risks related to the use of a medicine. The RMP would include an overview of the safety profile of the medicine, a pharmacovigilance plan, and a risk-minimization plan and would be designed to increase the likelihood of the medicine's benefits exceeding its risks by the greatest achievable margin. More recently, experts across the region convened to develop a consensus statement for use of biosimilars to treat moderate to severe psoriasis,[40] while considering

the complexities of the regulatory landscape and key therapeutic issues. The Latin American Forum on Biosimilars (FLAB) has also issued a position statement on biosimilarity, interchangeability, and extrapolation of indications,[25] based on a critical analysis of the available scientific and medical information available in the region.

Structural Characterization of Biosimilars

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[41] FDA,[42] and EMA[43] have all issued guidance on test procedures and quality considerations when assessing similarity for the development of biosimilar products. These guidelines reflect the scientific principles described in the ICH documents Q6B[41] and Q5E[44] for the assessment of the comparability of a biological product before and after a manufacturing process change made by the same manufacturer. They also recognize that assessment of biosimilarity between a proposed product and its reference product will be more complex and will likely require more extensive and comprehensive data. While the minimum requirement for biosimilarity of a protein product is that the amino acid sequences are identical, the assessment also needs to take into account the differences between the proposed biosimilar and the reference product that arise from various posttranslational modifications.

Currently, there are several biosimilars for rheumatic diseases approved (or under review) by the FDA or EMA that have been developed in line with these recommendations, including SB4[45] and GP2015[46] for etanercept; CT-P13,[47] SB2,[48] and PF-06438179[49] for infliximab; ABP 501,[50] BI 695501,[51] SB5,[52] and GP2017[53] for adalimumab; and GP2013[54] and CT-P10[55] for rituximab.

For intended copies, data to support claims of structural and biochemical comparability with innovator biologics are limited by definition and in some cases insufficient to indicate similarity with the innovator product. For example, a recent comparative assessment of multiple batches of 7 intended copies of etanercept found that none met the criteria routinely applied for comparability with the innovator product.[14]

Small structural differences between biosimilars and innovator products can have functional implications. For example, a lower level of afucosylation of the biosmilar CT-P13 compared with innovator infliximab was associated with a lower antibody-dependent cell-mediated cytotoxicity activity in the most sensitive version of the assay.[56] This finding raised debate concerning extrapolation of indications for CT-P13 to inflammatory bowel disease, but additional studies, conducted under more physiologically representative conditions, were sufficient to satisfy the EMA that there would be no meaningful clinical impact arising from this structural difference.[57] Therefore, understanding the possible clinical impact of small structural differences between proposed biosimilars and the innovator products may not always be possible by analytical studies alone. Clinical studies of CT-P13 in patients with RA and AS (PLANETRA[58] and PLANETAS[59]) convinced the FDA,[60] as well as Health Canada,[61] the regulatory authority of Canada, that the existing clinical data can be used to extrapolate the RA indication to the indications of the irritable bowel disease.

Clinical Assessment of Biosimilars

Initial clinical evaluation of biosimilars generally includes studies in healthy volunteers in order to demonstrate that PK and PD are comparable to those of the innovator molecule.[62] Pharmacokinetic equivalence is necessary, but not sufficient, to demonstrate biosimilarity; therefore, these initial evaluations may also include safety outcomes, particularly those related to immunogenicity.[9] (Studies in healthy volunteers are generally favored over patient populations at this stage because the patients' immune status may compromise the detection of potential differences in immunogenicity between treatments.) A number of approved or proposed biosimilars that have been developed based on the WHO-recommended approval pathway underwent this phase 1 evaluation and include biosimilars or proposed biosimilars of etanercept,[62–64] infliximab,[65–67] adalimumab,[68,69] and rituximab.[70] The products without relevant PK/PD information available can be regarded only as intended copies (e.g., TunEx,[71] Infinitam,[72,73] and Yisaipu[74]). (The link to Yisaipu prescribing information is no longer active. We last accessed it on December 18, 2017.)

Once PK comparability is confirmed, therapeutic similarity is determined in head-to-head studies in patients using an equivalence design, although a noninferiority design could be used under appropriate circumstances. The prespecified equivalence margins are based on historical data for the innovator product[75,76] and ultimately agreed upon with the relevant regulatory authority. The trial design of phase 3 comparability studies for biosimilars has been reviewed in a number of publications.[77–83] Currently, acceptable evidence of biosimilars' safety and efficacy stems from randomized, double-blind, active-controlled, parallel-group, equivalence or noninferiority trials, with indications, patient populations, background therapies, stratification factors, and outcome measures selected in a way that facilitates the detection of potential differences between the originator and the proposed biosimilar.[77–83] Importantly, the body of evidence needed for approval may differ between biosimilars,[78] which reflects the reality of complex molecules that are being compared. In addition, it should be pointed out that biosimilarity is not a transitive property: that is, the fact that 2 biosimilars are sufficiently similar to the originator does not mean that they are sufficiently similar to each other.[79]

Of note, the ability to switch between innovator product and biosimilar is a key consideration for practicing clinicians. Switching is usually not required to be tested as part of the approval pathway, but this aspect is increasingly being incorporated into phase 3 studies of biosimilars. The guiding principle behind the approval requirements for biosimilars adopted by the EMA[7] and the FDA[6] is the expectation that exchanging the innovator biologic for a biosimilar will not adversely affect clinical outcomes or safety. Although these requirements include supportive evidence for switching between treatments, there is a need for more extensive switching information for biosimilars, including the safety and efficacy of switching back to the originator product, and potentially, between the biosimilars themselves. Therefore, it would be beneficial if an accepted standard existed for the design of adequately powered switching studies, which would incorporate elements, such as a randomized design with appropriate control arms (including at least 1 switching arm), evaluation of immunogenicity, and sufficiently long washout and follow-up periods.[84]

Phase 3 studies conducted in line with the FDA and EMA guidelines include those for biosimilars or proposed biosimilars of etanercept (SB4,[85] GP2015,[86] and CHS-0214[65]), infliximab (CT-P13[87] and SB2[88]), adalimumab (ABP 501[89] and SB5[90]), and rituximab (PF-05280586[91] and GP2013[92]). In 2016, based on a critical analysis of the available data, the FLAB concluded that, among the biological molecules marketed in Latin America, only CT-P13 can be considered a true biosimilar.[25] In addition, Brenzys (SB4) was licensed in Brazil in 2017, which brings the total number of true biosimilars approved for rheumatic diseases in Latin America to 2 (Table 1).[93]

Of note, phase 3 clinical trials of intended copies are generally not available in the peer-reviewed literature. Those that have

TABLE 1. Biosimilars and Intended Copies Available in Latin America in 2018 for the Treatment of Rheumatic Diseases

Product Name	Originator Biologic	Indications	Countries Marketed	Adequate Phase 3 Data Available
Biosimilars				
Remsima (CT-P13)	Infliximab	Rheumatoid arthritis, ankylosing spondylitis, Crohn disease, psoriasis, psoriatic arthritis, ulcerative colitis	Argentina, Brazil, Chile, Colombia, Mexico, Venezuela	Yes
Brenzys (SB4)	Etanercept	Rheumatoid arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, psoriasis, psoriatic arthritis	Brazil	Yes
Intended Copies				
Etanar	Etanercept	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	Colombia	No
Etart	Etanercept	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	Mexico	No
Infinitam	Etanercept	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	Mexico	No
Kikuzubam	Rituximab	Rheumatoid arthritis, non-Hodgkin lymphoma, leukemia	Mexico (withdrawn in March 2014)	No
Novex (Tasiur[a])	Rituximab	Rheumatoid arthritis, non-Hodgkin lymphoma, leukemia	Argentina, Dominican Republic (Tasiur[a]), Mexico, Paraguay, Uruguay	No
Reditux/Tidecron	Rituximab	Rheumatoid arthritis, non-Hodgkin lymphoma, leukemia	Bolivia, Chile, Ecuador, Paraguay, Peru	No
Usmal	Rituximab	Rheumatoid arthritis, non-Hodgkin lymphoma, leukemia	Bolivia, Honduras	No

[a]Tasiur was withdrawn from the market in Dominican Republic in 2018.

Adapted from a Generics and Biosimilars Initiative table.[93]

been reported (e.g., for Infinitam,[72,73] Anbainuo,[94,95] and Reditux[96]) usually did not use the innovator product as the comparator, which hinders an adequate assessment of biosimilarity. For instance, an open-label, prospective, single-arm, multicenter study of Etacept, an intended copy of etanercept, in patients with moderate to severe, active RA who had shown inadequate response to DMARDs (N = 98) was associated with the American College of Rheumatology 20% improvement (ACR20 response) in 76% of participants, but these data are available only in the Etacept prescribing information[97] and remain unpublished in peer-reviewed literature. Similarly, a randomized, 12-week, open-label study of Intacept,[98] in which patients with active RA were assigned to the innovator product etanercept (n = 25) or Intacept (n = 87), resulted in ACR20 responses of 84% in both treatment arms,[99] but these findings also remain unpublished. The prescribing information for Yisaipu, another intended copy of etanercept,[100] refers to two 12-week, methotrexate-controlled, multicenter clinical trials, one conducted in patients with moderate to severe, active RA (N = 238) and the other in patients with moderate to severe plaque psoriasis (N = 144). A third study has been conducted in patients with active ankylosing spondylitis (N = 141), who were randomized to receive Yisaipu or placebo in a double-blind manner for 6 weeks, followed by open-label treatment with Yisaipu for additional 6 weeks. After 6 weeks of the double-blind treatment, a significantly higher proportion of patients in the Yisaipu group (68%) were reported to have achieved an ASAS20 response, compared with those in the placebo arm (55%; $P < 0.001$). (The link to Yisaipu prescribing information is no longer active. It was last accessed on December 18, 2017.) An identical study is described in the Etacept prescribing information,[97] suggesting that Etacept and Yisaipu are produced by the same manufacturer. Safety and efficacy of Altebrel and etanercept have been deemed comparable based on a noninferiority, randomized, double-blind, parallel-group clinical trial in patients with active RA (N = 128),[101] but this study also has not been published in the peer-reviewed literature.

Clinical Implications of the Introduction of Biosimilars and Intended Copies

Both the FDA[102] and the EMA[103] have pharmacovigilance mechanisms in place to monitor the real-word experience with biosimilars.

So far, real-world evidence for efficacy and safety of biosimilars is scarce. A 6-month observational study of Italian patients with spondyloarthritis who were switched from infliximab to CT-P13 (N = 41)[104,105] did not show a difference in disease activity parameters, safety, or immunogenicity between the reference product and the biosimilar[104]; a similarly designed study of patients with various rheumatic diseases conducted in Finland yielded similar results.[105] In addition, a study of 2030 Danish patients, 80% of whom were switched from etanercept to SB4 for economic reasons, showed that 18% of switched patients discontinued SB4 treatment within 1 year (mostly due to adverse events [AEs] or lack of efficacy).[106]

There have been more reports on real-world data for intended copies, which have been available in some markets for longer than biosimilars. In a 20-week, observational, single-arm study of Etanar in patients with active RA despite DMARD therapy (N = 110),[107] significant improvements from baseline in disease activity (DAS28) and patient functioning (Health Assessment

Questionnaire) were reported. In another observational cohort study of Etanar, Colombian patients with active RA despite DMARD treatment (N = 105) had a significant improvement in disease control (assessed using ACR20 and DAS28) after 12 months of treatment, compared with historical 12-month data.[108] The open-label design, few details on the patient characteristics, and lack of comparator arm limit meaningful comparison of Etanar with etanercept. Etanar has been compared with adalimumab and infliximab in a cross-sectional cohort study in patients with established RA in Colombia (N = 158) and found to be as effective as the comparator biologics in controlling disease activity, with fewer AEs.[109] A single-arm study of Etacept in patients with axial spondyloarthritis (N = 25) showed improvements in measures of disease activity over 12 weeks of treatment,[110] again without using an etanercept comparator arm. The results of a 6-month, single-center trial from India (N = 69; not powered to test for equivalence), in which children with juvenile idiopathic arthritis were treated with Cipla, Intas, or etanercept, showed similar efficacy and safety between the intended copies and the reference product.[111] Finally, a preliminary analysis of patients from Mexico and Colombia with various rheumatic diseases (enrolled, N = 219; analyzed, n = 118) treated with intended copies of etanercept (Infinitam, Etanar, n = 14) or rituximab (Kikuzubam, n = 205) and followed up from treatment initiation to the occurrence of the first AE found that 17% of patients experienced grade 3 or 4 AEs, with a short time of onset.[112]

Practical Aspects of Considering a Biosimilar

The availability of biosimilars has increased the number of treatment options available to rheumatologists, prompting the need for additional considerations in their clinical decision making. Whether considering initiating patients on an innovator biologic or biosimilar or switching biologic-experienced patients to a different biologic product, clinicians should be sufficiently aware of the preclinical and clinical data underlying the products' approval. This should include the evidence of safe and effective switching from one product to another. While such information may be available for biosimilars approved according to WHO recommendations,[4] some biologics marketed in Latin American countries were approved through a process less than adequate for these types of products.

The motives for selecting a biosimilar over the innovator product, either as an initial or switched-to treatment, are unlikely to be driven by clinical considerations. Instead, the decision to choose a biosimilar is chiefly driven by cost, particularly in countries where lower-cost alternatives are mandated by health authorities. Therefore, clinicians must be prepared to explain reasons for such a move to their patients, who otherwise may be satisfied with their existing treatment. In addition, any proposal to switch treatments must take into account the indirect costs of additional training, which may be required to gain familiarity with the new delivery device. Finally, selecting an intended copy instead of a biosimilar should be considered a high-risk approach, because of a less rigorous pathway of bringing intended copies to market.

CONCLUSIONS AND FUTURE DIRECTIONS

In all Latin American countries, the approval process for biosimilars should be harmonized with the WHO recommendations.[4] In other words, the status of biosimilarity should be granted only after a comparability exercise and an assessment of the totality of evidence have been completed, which should include head-to-head preclinical and clinical comparisons with the innovator product. In addition, the "biosimilar" agents already on the market that gained approval with insufficient data or through an inadequate approval process should be reevaluated in order to be relicensed, with manufacturers providing the necessary evidence to demonstrate similarity to the innovator product.

As more biosimilars become available, appropriate postmarketing evaluation is essential to enable monitoring of risk. In particular, the pharmacovigilance programs could capture potential AEs that were never (or rarely) associated with the innovator product. Inclusion of approved biosimilars in biologic registries in order to accumulate real-world data would expand body of evidence that could be used for comparative assessments with the innovator product, thereby facilitating clinical decision making when selecting optimal treatment for each patient.

Extrapolating a biosimilar's approval to all the indications authorized for the originator, but for which clinical data with the biosimilar are not available, is a common practice of many health authorities.[113] In addition, once approved, the biosimilar could be designated an interchangeable innovator biologic product, which means that it could be used as a substitute for the reference product without intervention of the prescribing physician or additional training. (The concept of interchangeability is different from switching because the latter is initiated by the prescribing physician or even the patient.) This system could work only if the approval process for biosimilars is sufficiently rigorous.[114] Currently, in many countries, including the United States, interchangeability requires additional studies, review, and approval beyond that required for biosimilarity. Because of the very heterogeneous regulatory landscape in Latin America, each designation of interchangeability will need to be evaluated independently, especially because more biosimilars of the same innovator product become available and substituting one biosimilar with another becomes a realistic possibility. However, we think that the costs and complexity that would be associated with designing and conducting interchangeability trials make such studies unlikely.

Ultimately, clinicians in Latin America need to be well informed about the principles surrounding biosimilarity, the regulatory pathways adopted in their countries, and what they should expect in terms of the clinical characteristics of the biosimilars approved by their health authorities. Consequently, there is a need for education (beyond CME) to raise awareness of this topic, wherein regional or national health professional and scientific societies can play a part, which would enable clinicians to prescribe biosimilars in an optimal manner and could include paper- or web-based materials, as well as various forms of peer-to-peer interactions. It should be pointed out that educational efforts are in progress. For example, a working group operating within the Pan-American League of Associations for Rheumatology presented the following draft consensus recommendations for the approval and implementation of biosimilars for rheumatic diseases during the 20th Annual Pan-American League of Associations for Rheumatology Congress (Buenos Aires, Argentina, 2018)[115]:

1. Biosimilars should be considered for the treatment of rheumatic diseases once their biosimilarity has been demonstrated.
2. An effective pharmacovigilance program should be implemented applying activities to closely monitor, identify, and assess any safety concerns related to biosimilars.
3. Risk management plan for biosimilars approval should be required by regulatory agencies, and it should be the same as for reference products.
4. The implementation of registries is encouraged, in order to complement postapproval surveillance for safety concerns related to biosimilars.
5. A naming convention should be implemented to clearly identify specific products (both biosimilars and reference biologics).

6. Strategies to ensure traceability should be implemented to track all steps involved in the supply chain, enabling address association of adverse effects with a specific medication.
7. The price of biosimilars should be lower than that of the reference biologics, potentially enhancing access to high-cost rheumatology treatments.

Finally, although it would be impossible for each clinician to review in detail all the evidence supporting biosimilarity of each product of interest, we think that a good rule of thumb would be to ask the following questions:

1. Does the country have biosimilars guidelines in place?
2. Are the guidelines generally in agreement with the WHO recommendations?[4]
3. Are the adopted guidelines followed in regulatory practice?
4. If the guidelines are in place, has the biologic been approved *after* their adoption?
5. Does the manufacturer's submission include "the totality of evidence" (i.e., analytical and animal studies, clinical pharmacology, and the clinical data)?
6. Are the clinical studies published in peer-reviewed journals?
7. Does the biosimilar have switching data available, either from the pivotal or extension studies?

If the answer to all of those is affirmative, then the clinician can be reasonably confident that the minimum requirements for safety and efficacy of a biosimilar have been met. Conversely, a single negative answer should prompt more inquiries, which could be addressed at the local health authorities or professional associations.

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