

Comparing Originator Biologics and Biosimilars: A Review of the Relevant Issues



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ABSTRACT

Purpose: We provide a review of current knowledge on comparability between biosimilars and originator biologics in view of the continuous evolution occurring in this highly dynamic area.

Methods: English-language literature indexed in MEDLINE was explored, without time limits, to July 31, 2016, using the terms *biosimilar*, *biotechnologic drug*, *biologic drug*, *monoclonal antibody*, *fusion protein*, and *anti-tumor necrosis factor*. The reference lists of identified articles were examined carefully for additional pertinent publications.

Findings: Biological medicines are much more structurally complex and extremely sensitive to manufacturing conditions and therefore more difficult to characterize and produce than small molecule drugs. Even minor changes in manufacturing may lead to significant variations of the cellular systems used for biological production, as well as to differences in the structure, stability, or other quality aspects of the end product, all of which have the potential to affect tolerability and/or efficacy and increase the risk of immune responses. Owing to these issues, specific regulatory guidance on biosimilars is continuously evolving, and there is some disagreement on which studies need to be implemented to approve a biosimilar. According to current literature, the following points on biosimilars deserve consideration: biosimilar development is characterized by global harmonization, although several not fully answered questions remain regarding extrapolation of indications, switching or interchangeability, and tolerability; in patients with rheumatic diseases, the tolerability and efficacy of biosimilars in clinical practice remain to be established; several medical and patient associations have published position papers on biosimilars requesting that safety,

efficacy, and traceability be carefully considered; long-term postmarketing studies should be implemented to allow physicians to gain confidence in biosimilars.

Implications: On the basis of current knowledge, and taking into consideration both regulatory rules and medical society positions, it can be concluded that, although cost savings are highly desirable, the approval process for biosimilars needs to place tolerability and efficacy, supported by scientifically sound evidence, as the highest priority. Moreover, physicians must retain full authority regarding the decision about which biopharmaceutical to use for treating patients. (*Clin Ther.* 2017;39:1026–1039) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: biologics, biosimilars, comparability, manufacturing, regulatory guidance.

INTRODUCTION

The therapeutic success of biotechnological drugs, commonly designated as biologics, such as monoclonal antibodies (mAbs) and recombinant versions of endogenous proteins, is increasingly transforming the pharmaceutical market. Patent expiry of biologics (ie, originators) has also opened the field to the so-called biosimilars, medicines that are intended to be similar, although not identical, to the originator biologics in terms of quality, efficacy, and tolerability. It is undeniable that there are highly debated issues regarding biosimilars in immune-mediated inflammatory diseases: increasing demand for biologics given their

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clinical success, the nearing of patent expiry for the 4 top-selling biologic brands, and the search for reducing the economic burden of drugs.¹

A biologic medicine is a large molecule synthesized by cellular systems using recombinant DNA technology and used for treatment, diagnosis, or prevention of various diseases.² Current biologics include 3 main categories: (1) products almost identical to endogenous factors, often used as replacement therapy; (2) mAbs that bind soluble or cell surface targets, thus blocking cellular signaling pathways and related functional responses; and (3) engineered proteins mimicking receptors (eg, soluble receptors, receptor antagonists, fusion proteins). Biologics can be from 200 to 1000 times the size of small molecule drugs and are much more complex from a structural standpoint. Biologics are also extremely sensitive to manufacturing conditions and are therefore more difficult to characterize and produce than small molecule drugs.

Unlike generic medicines, in which the active ingredients are identical to their respective originators, biosimilars are similar, but not identical, to their originators. Minor differences among the active ingredients are allowed, provided they are not clinically meaningful. The European Medicines Agency (EMA) defines a biosimilar as a biological medicine that contains a version of the active substance of an already authorized original biologic (reference medicinal product; ie, the originator). Similarity to the originator in terms of quality, biological activity, tolerability, and efficacy, based on a comprehensive comparability exercise, needs to be established.³

Steps underlying biologic drug development and manufacturing are highly complex, sensitive to a number of determinants, and specific to a particular product. Even minor changes in manufacturing may lead to significant variations of the cellular systems used for biologic production, as well as differences in the structure, stability, and biology of the end product. Any variation has the potential to affect the tolerability and efficacy of the marketed product, as well as increasing the risk of adverse immune responses.

Of interest, regulatory guidance on biosimilars is continuously evolving, and there is still disagreement on which studies must be implemented to approve a biosimilar. Overall, uncertainties remain the key issue surrounding biosimilars. Policymakers, physicians, and other stakeholders must consider all the issues

raised by health authorities in this field. It is crucial to assess how closely similar biosimilars are or are not to their originators and how small differences may affect clinical outcomes.⁴ The present article reviews current knowledge on comparability between biosimilars and originators in view of the continuous evolution in this highly dynamic area.

DEVELOPING AND MANUFACTURING OF BIOLOGICS

Biologics comprise a wide array of substances synthesized by cell systems using different processes, including recombinant DNA technology, controlled gene expression, and antibody technologies. To better appreciate differences between originators and biosimilars, it is important to consider the molecular complexity of biologics and their complex manufacturing that involves several steps.

mAbs

Mice were the first source for producing mAbs endowed with high affinity and specificity for their molecular targets. However, the use of rodent mAbs as therapeutic agents has been hampered by their inherent high risk of immunogenicity. Different technologies were then explored attempting to generate low immunogenic mAbs, starting with chimeric antibodies and progressively moving toward humanized and then fully human antibodies.

Technology of Phage Display for Fully Human mAbs

Phage display allows for selection of antigen binding fragments (Fabs) of human mAbs through in vitro procedures, without in vivo steps. It relies on the generation of a library of antibody human genes cloned into the DNA of an *Escherichia coli* phagemid, a bacterial virus that, once introduced into bacterial cells, replicates autonomously, allowing for the biosynthesis of Fabs. On replication, the phage will expose the Fab on its surface and carry the respective DNA encoded in the phagemid DNA. Therefore, with this technique, the genotype and phenotype of specific human Fabs are coupled in the same recombinant phagemid.^{5,6}

Technology of Transgenic Mice for Fully Human mAbs

Another technique that has significantly contributed to the development of fully human mAbs relies

on the use of transgenic mice expressing human antibody gene sequences. These mice are manipulated to disrupt their own genes coding for immunoglobulins and replace them with DNA encoding human antibodies.^{7,8} When transgenic mice are challenged with the antigen of interest, they are prompted to produce human antibodies via physiologic processes that include affinity maturation. Fully human mAbs can be then developed using conventional fusion technology or even phage display technology.^{5,8}

Fusion Proteins

A number of biologics are fusion proteins in which the extracellular domain of a receptor has been fused with the Fc region of an immunoglobulin, usually a human IgG1, to generate a soluble form of the receptor. Etanercept is the best recognized example in rheumatologic practice because it is a soluble form of the p75 tumor necrosis factor (TNF) receptor that can bind and neutralize TNF.⁹ Fusion proteins are relatively simple to design and can exploit the ligand redundancy of certain receptors, providing a broader specificity than antiligand or antireceptor mAbs.

Posttranslational Phase of Protein Biosynthesis in Biologic Manufacturing

The pharmacologic action of biologics will depend not only on their amino acid sequence (primary structure) but also on their secondary, tertiary, and, in several cases, quaternary structures. In the posttranslational phase of biosynthesis, the pharmacologic properties of biologics can be significantly affected by their conjugation with a variety of chemical moieties, including mostly sugars (glycosylation) or phosphates (phosphorylation). Owing to associations between structure and function, clinically meaningful differences in therapeutic and immunogenic activities may result from changes in the posttranslational phase. There is, indeed, a strong association between manufacturing processes and physicochemical and biological properties of the end product, which are very sensitive to production conditions. Thus, even very small changes in manufacturing can have significant impact on quality, biologic properties, and clinical activity of the final product. Accordingly, there is consistent evidence that even a small discrepancy at each step (involving for instance the purification process or the molecular site of posttranslational glycosylation) can lead to significant variations of

the end product, which might cause significant changes in clinical outcomes.^{10,11}

As mentioned above, the manufacturing process of a biologic cannot be duplicated exactly by another manufacturer; therefore, an originator and biosimilar may display a number of differences.^{12,13} Because biologics are not produced by chemistry but are developed in cell systems, it is not possible to generate identical copies of the active substance. Biologics are produced in genetically engineered cell systems in highly controlled environments; therefore, the protein of interest produced by cultured cells will be influenced by cell features, the environment, and nutrients. Each manufacturer establishes specific processes that confer distinctive physicochemical and pharmacologic properties to the end product.

Heterogeneity of Biologics

Unlike small molecule drugs, produced by chemical synthesis, biologics have several aspects of heterogeneity related to host cells, viral vectors used for transfection, cell growth conditions, and purification processes. All these procedures and related materials introduce determinants of variability that cannot be translated from one manufacturer to others. Indeed, the production process of biologics is so unique that it has been stated that “the product is the production process.”¹⁴ As mentioned above, biosimilar manufacturing is not as straightforward as with generics. The concept that a biologic might lose its status of biosimilarity as a result of an amino acid substitution is critical, particularly because mAbs and fusion proteins are complex polypeptides that undergo considerable posttranscriptional modifications. They are produced by cell systems, and, depending on the clone and production process, microvariations, such as asparagine deamidation or isoaspartic acid isomerization, may occur with significant putative consequences in higher-order structure and target binding.¹⁵ Moreover, biosimilars might differ slightly from originators in terms of host cell protein impurities, immunogenicity, and other attributes. Some of these differences can depend on the manufacturing process (raw materials, gene expression system, fermentation, purification, formulation, and packaging). In this respect, biosimilars cannot be designated as biogenerics (based only on analytical considerations and simple pharmacokinetic data; eg, bioavailability and bioequivalence).^{16,17}

Structural differences between biosimilar and originator are generally acceptable if such differences do not significantly affect clinical performance. This is a very important concept because a wide variability in product composition and bioactivity has been documented with some presumed biosimilar products, particularly those marketed outside the United States and the European Union. For these reasons, regulatory guidelines governing the development of biosimilars take into account inherent differences and require that rigorous pharmacovigilance programs be implemented throughout the postmarketing phase. Furthermore, because of complexities of the manufacturing process, there is a potential for heterogeneity in terms of biosimilar quality.¹⁸

It has been argued that originators themselves may change over time in their features because of minor changes in their manufacturing process, ending up by becoming biosimilars of themselves. However, several long-term clinical trials and postmarketing surveillance programs, reaching up to >10 years of follow-up for the oldest biologics, such as adalimumab, have found that their clinical performance, in terms of both efficacy and tolerability, has remained stable over time.^{19–22}

Immunogenicity

All biologics have an immunogenic potential, and several guidelines and regulatory documents are aimed at assisting physicians in assessing the risk level of unwanted immunogenicity. The causes of immunogenicity are undoubtedly multifactorial but not yet fully understood. The current expert opinion is that the assessment of unwanted immunogenicity can be improved by prediction tools, optimizing the performance of immunogenicity assays, and learning from the clinical effect of other biologics previously administered to patients.²³

The molecular structure and production process of biologics play an important role in determining their immunogenic potential, which may affect both efficacy and tolerability. Although the EMA and US Food and Drug Administration (FDA) have published helpful guidance on immunogenicity, product-specific considerations make it difficult to define a common approach for different biologics, particularly when considering mAbs. As a consequence, it appears crucial that each manufacturer justifies the method used to assess similar immunogenicity. Indeed,

immunogenicity can be influenced by several factors (eg, a different pattern of glycosylation can expose or hide antigenic epitopes).²⁴

Chamberlain⁹ recently reviewed current methodologic limitations in assessing the respective immunogenicity of biosimilar and originator mAbs, emphasizing the relevance of a correlation between bioanalytical parameters and appropriate clinical end points. He also underlined the possible need for postmarketing studies to better appreciate the effect of differences in the incidence of antidrug antibodies (ADAs). Given current uncertainties concerning the long-term clinical effect of immunogenicity for originators, there can be no predefined margin for an acceptable difference based on the incidence and magnitude of ADA detection. Therefore, it is suggested that any differences be assessed with regard to clinical parameters and the designation of biosimilarity given with reference to similarity in direct comparative quality, nonclinical, and clinical evaluations. Thus, there is a need for a totality of evidence approach.²⁵

When mAbs are administered to patients, these biodrugs may behave as non-self-antigens, reflecting their distinctive molecular properties and manufacturing procedures. All these determinants can generate mAb heterogeneity, which may contribute to immunogenicity. The generation of ADAs can be followed by a decrease in mAb pharmacodynamic activity or bioavailability.^{26,27} ADAs may behave as neutralizing antibodies, able to block the mAb active site, or they can target other mAb domains that, while not affecting the antigen-binding capacity, may accelerate mAb clearance.²⁸ In the latter setting, the presence of circulating ADAs can affect the amount of bioavailable mAb in the blood, thereby impairing its therapeutic potential.^{29–33} In addition, the formation of ADA-mAb immune complexes has been associated with the occurrence of adverse immune effects (both local and systemic in nature).²⁵

Clinical data clearly indicate that ADAs have the potential to influence the efficacy of mAb therapy in rheumatoid arthritis (RA), ankylosing spondylitis, and inflammatory bowel diseases (IBDs). Even though ADA induction has not been investigated rigorously for all originators, it has been widely observed in patients with immune-mediated inflammatory diseases treated with TNF inhibitors.^{34,35} The results of the Programme Evaluating the Autoimmune Disease

Investigational Drug cT-p13 in Ankylosing Spondylitis Patients (PLANETAS) and Programme Evaluating the Autoimmune Disease Investigational Drug cT-p13 in Rheumatoid Arthritis Patients (PLANETRA) trials highlighted differences in the development of ADAs after administration of CT-P13 (infliximab biosimilar) to patients with RA or ankylosing spondylitis.^{36–39} These immunogenicity data provide further insights into the relatively high frequency of ADAs and the influence of underlying disease on ADA induction.

On the basis of the above discussion and with the goal of identifying clinically meaningful differences in immunogenicity, some inferences have been drawn on the type and amount of evidence that is critical for assessment of biosimilarity. Because different mAbs have distinct risk profiles, there may be differences in the type or extent of data required to conclude that an increase in immunogenicity of a biosimilar has no negative effect on the overall clinical benefit and risk. In particular, a comparative clinical study for each therapeutic indication, powered to exhibit therapeutic equivalence, is suggested to enable adequate identification of a clinically meaningful effect, provided the study population represents a sensitive model.

THE EVOLVING REGULATORY LANDSCAPE FOR BIOSIMILARS

Regulatory guidelines for biosimilar development are well defined but are also subject to continuous revision. Regulators follow up closely the variations introduced over time into the originator as a consequence of manufacturing changes. The EMA first established a regulatory pathway for the approval of biosimilars in 2005, taking a conservative approach. Since then, guidelines have been updated and revised several times, and a specific guideline for mAb biosimilars was issued in 2013.^{3,40–43} Besides providing overarching guidance, the EMA has issued specific annexes or class guidance that indicates what data must be provided to obtain biosimilar approval. In the United States, there are now several FDA guidance documents that address the development and production of biosimilars.^{44–50}

The process of biosimilar approval requires evidence of comparability in terms of quality, efficacy, and tolerability between biosimilar and reference product (originator). Such evidence must be provided by undertaking a stepwise comparative procedure

based on nonclinical and clinical evaluations. The most recent revision of the EMA guideline, addressing the general principles for nonclinical and clinical development of biosimilars,³ discusses several topics, including the use of pharmacodynamic markers, the choice of appropriate patient population and surrogate or clinical end points in efficacy trials, the appropriate design of immunogenicity studies, and the requirement of postmarketing risk management plans and pharmacovigilance programs.⁵¹

Comparability Exercise

The key to biosimilar approval in the European Union lies in comparability exercises between biosimilar and originator: physicochemical and biological comparability (quality studies), preclinical comparability (in vitro and in vivo studies), and clinical comparability. The clinical comparability exercise is usually a stepwise procedure that should begin with pharmacokinetic and, if feasible, pharmacodynamic studies, followed by at least one efficacy and tolerability clinical trial. In particular, clinical comparability will be normal in randomized, blinded Phase III trials. It is suggested that an equivalence trial design should be used in a sensitive population of patients with a disease for which the originator is licensed.³

Within the frame of comparability exercise, the potential for biosimilar immunogenicity should also be investigated in a comparative manner to the originator. The type and amount of immunogenicity data will depend on the experience gained with the originator and its class. An evidence of increased immunogenicity, compared with the originator, may become an issue for risk-benefit analysis and can question the request for biosimilar approval.

Extrapolation of Indications

One of the most controversial issues with biosimilars is the extrapolation of therapeutic indications: are data obtained from patients with one clinical indication sufficient to allow the biosimilar use in patients with other indications, for which direct clinical trial evidence is not available? Most experts agree that a biosimilar effective for one therapeutic indication may not necessarily be effective for another indication for which the originator had been previously approved.⁵²

European regulation requires that extrapolation of efficacy and tolerability from the therapeutic indication subjected to clinical investigation to other

therapeutic indications be properly justified considering the totality of data (ie, quality, nonclinical, and clinical comparative data). In particular, according to the EMA requirements, the following major criteria must be satisfied: (1) the mechanism of action of the originator is the same across all the indications intended for extrapolation; (2) equivalence and clinical comparative studies have been performed in the most sensitive therapeutic indication; and (3) the most sensitive indication should ideally be the one that is able to produce clinically relevant differences in terms of key efficacy and tolerability, including immunogenicity, parameters.² Whenever it remains unclear that the tolerability and efficacy profiles, as documented for one indication, would be relevant for another indication, additional data will be required.³ In the United States, if a biosimilar is not approved initially for all indications granted to the originator, the biosimilar manufacturer must conduct clinical trials for each therapeutic indication to support a license application for each indication. Likewise, if the originator is approved for an additional indication after its biosimilar has been licensed, the procedure of the extrapolation of indication no longer applies. An additional issue is represented by extrapolation to patient ages that are different from those involved in the registration trials.

Even when the regulatory authorities grant licensing to a biosimilar for extrapolated therapeutic indications, clinicians might be reluctant to acknowledge this approval. This issue has been matter of considerable debate after the approval of biosimilar infliximab by the EMA, which extrapolated to this product all the therapeutic indications previously granted to the originator, in both adults and children, after 2 comparative trials in patients with ankylosing spondylitis and RA. Even if the EMA has established clear criteria for extrapolating therapeutic indications, this decision has been challenged by several authors based on the following arguments: (1) RA is not the most sensitive clinical condition (lower efficacy margin against placebo in RA; use of lower doses in RA vs other therapeutic indications; use of infliximab in combination with methotrexate in RA) and (2) among the immune-mediated inflammatory diseases, patients with RA do not represent the most sensitive population for the development of immunogenic responses.⁵² These arguments may explain why several experts have argued that convincing data from clinical trials

are needed for each individual indication^{53–60} and why the EMA has recommended the implementation of a comparative randomized clinical trial of originator and biosimilar infliximab in patients with Crohn disease.

Nomenclature

To ensure accurate prescribing and avoid confusion among biosimilars and originators in the postmarketing setting, a specific nomenclature is required to distinguish biosimilars from their originators and from each other. To achieve this goal, international nonproprietary names (INNs) should not be used as the only means for biologic identification. Advocates for a unique naming system of biosimilars claim that, if a common nonproprietary name were used, it would be difficult to ascribe adverse events to a specific product.³⁷ Instead, it would be more appropriate to use the brand name, the INN plus the brand name, or some other unique identifier. In this respect, it has been suggested that a Greek letter or a combination of several letters could be appended to the end of INNs of biologics.⁶¹ Alternatively, a biologic qualifier (a 4-digit code proposed by the World Health Organization) could be used to distinguish originators from biosimilars.⁶² In 2012, the European Commission issued the Directive 2012/52/EU, which requires the use of brand names “to ensure clear identification of biological medicinal products,”⁶³ a requirement that also applies to biosimilars. In addition, since adverse events might depend on unintentional changes during manufacturing (production drift), besides the brand name, it is also suggested that the batch number should be notified to the regulatory authority to ensure proper traceability. In this respect, a survey by Vermeer et al⁶⁴ on reports of suspected adverse reactions to biopharmaceuticals in the US and European databases found that physicians, although reporting brand names, disregarded the indication of batch numbers in most cases.

Pharmacovigilance

Pharmacovigilance, in terms of postmarketing surveillance, is crucial for biosimilars. Data from preregistrational clinical studies are usually insufficient to identify rare adverse effects. Actually, the clinical development program of biosimilars is shorter compared with originators and thus less suitable to adequately identify tolerability risks. Therefore, it is

recommended that the clinical tolerability of biosimilars be closely monitored on an ongoing basis during the postmarketing phase.³

Accordingly, within the authorization procedure, the applicant should present a description of the pharmacovigilance program and a risk management plan in accordance with current EU legislation and pharmacovigilance guidelines. Any specific tolerability monitoring imposed on the originator or medicinal class should be adequately addressed in the pharmacovigilance plan of the biosimilar, and immunogenicity should specifically be considered in this context. There is also a need for postmarketing observational studies to assess the effect of observed differences in the incidence of ADAs and magnitude on long-term treatment benefit. Such studies should be performed in both children and adults because toxic effects and long-term sequelae may differ. Data collection by organizations outside the pharmaceutical industry has also proven to be reliable across different national registries⁶⁵ and has been requested by rheumatology societies, such as the American College of Rheumatology (ACR).⁶⁶

SWITCHING, INTERCHANGEABILITY, AND SUBSTITUABILITY

Switching

Drug switching means that a patient is transitioned from one biologic to another or from an originator to its biosimilar (or vice versa). With respect to switching between an originator and its biosimilar, several considerations are relevant to clinical practice. Switching among biologic therapies is common practice in patients with RA who have an inadequate response or develop adverse events: the use of sequential biologic therapy for these reasons is supported by observational studies and guidelines. However, economic constraints have recently prompted switches to biosimilars in patients who are well controlled with their current biologic therapy, despite limited evidence supporting this practice. Few trials have directly compared patients switched to a biosimilar with those continuing to take the originator. The 30-week PLANETRA and PLANETAS trials and their extension phases found no statistically significant difference between infliximab and CT-P13 in terms of efficacy and tolerability. However, current data refer to relatively small numbers of patients and do not

provide sufficient information on long-term efficacy and safety or frequency of rare adverse events. For example, ADAs that affect clinical efficacy are known to generally appear, at least in patients with RA, even after 1 year.^{38,39,67–71} Furthermore, an adequate sample size could have made some statistically significant differences in efficacy, at least in the PLANETAS extension study.

Reynolds et al⁷² accurately reviewed the switching issue, making a clear difference between switching for clinical reasons, which may include sequential treatments with different TNF antagonists or changing the biologic class, and switching for nonclinical reasons, driven by restrictions of health care budgets. Most rheumatologists currently switch between anti-TNF biologics when clinically indicated, according to clinical practice that is rapidly changing, as new biologics, endowed with novel mechanisms of action, are entering the pharmaceutical market and physicians are gaining experience with their use. Currently, switching exclusively among TNF antagonists and among agents of different biologic classes, in the presence of a lack or loss of efficacy or owing to tolerability issues, is considered to be clinically justified. On the other hand, switching for nonclinical reasons, despite the lack of data to support this practice and the considerable amount of data supporting clinically meaningful differences among biologics, cannot be endorsed. It must be taken into consideration that switching for nonclinical reasons might expand in the near future as regulatory bodies are continuing to approve biosimilars for clinical use. However, consistent evidence is needed to support this approach, and the potential economic consequences of cycling among therapies in good responders should also be considered.

Interchangeability

According to the World Health Organization definition, an interchangeable pharmaceutical product is “a product that is expected to have the same clinical effect as the comparator product and can replace it in clinical practice.”⁷³ In the United States, the term *interchangeable* also refers to biosimilar products that “may be substituted for the reference product without the intervention of the physician who prescribed the latter.” In the United States, a biosimilar can be considered interchangeable with the originator if a clinical trial has not revealed a loss of efficacy and an

increase in tolerability risk after at least a single switch from the originator.⁷⁴ However, interchangeability would require testing of repeated switches between originator and biosimilar. In the European Union, the EMA does not designate biosimilars as interchangeable; rather, this decision is left to national regulatory agencies.²

Unlike small-molecule drugs, an originator that is repeatedly interchanged with a biosimilar might elicit immunogenic responses that could compromise the efficacy and tolerability of both medications. Thus, frequent switching between originator and biosimilar should be avoided because even subtle differences, such as manufacturing impurities, could trigger an immune response.³⁷ This issue is particularly critical when treating patients with rheumatic diseases, who have a long life expectancy and typically face long-term therapies. The ACR position statement on biosimilars clearly states that prescribing physicians “must retain the right to write ‘dispense as written’ for all prescriptions” and raises concerns that repeated switching could carry too many uncertainties.⁶⁶ Likewise, a number of European medical societies, some of which agree with patient groups (such as the European League Against Rheumatism [EULAR] Standing Committee of People with Arthritis and Rheumatism), have issued documents that articulate their opposition to automatic substitution and multiple switching.^{24,75}

In the hemato-oncologic field, concerns about tolerability and efficacy have been claimed for biosimilar filgrastim and epoetins.⁷⁶ Epoetins were among the first approved biosimilars. The major concern with epoetins is the development of neutralizing, cross-reacting anti-epoetin antibodies that can cause pure red cell aplasia. It is still debated why the biosimilar molecule becomes immunogenic and whether such an effect may be related to manufacturing or other unknown circumstances.⁷⁷

Last, but not the least, interchangeability may significantly affect pharmacovigilance programs, possibly generating confusion among biosimilars and their originators during postmarketing surveillance.²⁴

Substitutability

For small-molecule drugs, substitution refers to the replacement of one medicine with another, often at a lower cost for the health service or the patient, which has the same qualitative and quantitative

composition of active substances, has the same pharmaceutical form and route of administration, and is bioequivalent to the reference medicine on the basis of appropriate bioavailability studies. Automatic substitutability refers to the practice by which a pharmacist may, or must, according to national or local regulations, dispense a drug that is equivalent and interchangeable instead of the prescribed branded medicine, without consulting the physician.

When considering biologics, the European legislation has entrusted to the national regulatory authorities of member states decision making and legislative autonomy about the automatic substitution of an originator with its biosimilar. However, the EMA has stated that the decision about the choice of prescribing a biosimilar in place of its originator must be entrusted to physicians.^{2,78} The Italian Medicines Agency (AIFA) has stated that originators and biosimilars cannot be considered merely as equivalent products and has thus excluded the practice of automatic substitution. However, the AIFA considers that biosimilars are not merely a therapeutic option available to physicians, but are to be preferred if they entail an economic advantage, especially for treatment of naive individuals. This statement introduces the concept of primary and secondary naive patients: primary naive are patients without previous therapeutic exposure to the originator, whereas secondary naive patients are those with previous exposure to the originator but with an adequately long washout period based on clinical judgment.^{79,80} Currently, there is an ongoing public consultation to update the AIFA position paper. However, in accordance with the concept of biosimilarity issued by the EMA, the principle of the dominant role of the prescribing clinician in choosing between an originator and its biosimilar must be emphasized.

Of note, the EULAR⁷⁵ and the ACR⁸¹ *do not recommend a switch during therapy with biologics* (see below), and the same position has been taken by the Italian Society of Rheumatology (SIR).²⁴

POSITION STATEMENTS OF MEDICAL ASSOCIATIONS

Many medical societies and other organizations have issued position statements, which indicate that

harmonization across countries is emerging with regard to the acceptance of biosimilars.

Position Paper of the SIR

The SIR has published 2 position papers,^{24,57} one of which was issued jointly with the Italian Society of Dermatology and the Italian Group of Inflammatory Bowel Disease. On the basis of literature review, the authors noted that clinical data are currently available only for RA and ankylosing spondylitis, referring to a relatively small number of patients, thus providing insufficient information on long-term efficacy as well as tolerability and frequency of rare adverse events. Conversely, direct evidence on efficacy, tolerability, and immunogenicity of biosimilars is still lacking in psoriasis, psoriatic arthritis, and IBDs, as well as in pediatric patients.

With regard to immunogenicity, the SIR position paper points out that longer observation periods are required than those reported in currently published data on biosimilars, because ADAs may develop after several infusions and sometimes even after 1 year of treatment. Considering the extrapolation of indications, the SIR states that there is no scientific evidence supporting automatic translation of therapeutic indications from an originator to its biosimilar, particularly because of the complex and different pharmacologic mechanism(s) of actions of a given biologic in the different approved clinical indications.

Overall, the SIR concluded that, given the limitations of current knowledge on biosimilar efficacy and tolerability, it is mandatory to provide specialists with rules and to perform ad hoc clinical trials and implement appropriate drug surveillance programs. Moreover, in line with the EMA and AIFA, the SIR recommends the use of biosimilars only in naive patients and agrees to avoid substituting originators for biosimilars and vice versa.

Position Statement of the ACR

The ACR states that they strongly believe that tolerable and effective treatments should be available to patients at the lowest possible cost.⁸¹ However, American rheumatologists also believe that decisions about biosimilarity and interchangeability must be driven by sound science that takes into account several observations and guiding principles. They recommend that long-term postmarketing registry-based data collection be established to monitor for

less common, but potentially important, adverse events and that the decision of substituting an interchangeable medicinal product should not be taken without support by the knowledge of prescribing physicians.

Position Statement of the American Academy of Dermatology

In November 2012, the American Academy of Dermatology updated its position statement on generic and biosimilar substitution to reflect its views, with particular regard to the interchangeability of biosimilars.⁸² The American Academy of Dermatology advocates prohibiting biosimilar substitution unless all of the following minimal thresholds are met: (1) the biosimilar has a unique nonproprietary name to eliminate confusion, to allow practitioners to accurately track therapy in a patient's permanent record, and to allow for the collection of adverse event information; (2) the biosimilar has been designated by the FDA as interchangeable with the prescribed originator for the specified, indicated use; (3) the prescribing physician provides explicit permission to the pharmacist that a biosimilar may be used as a substitute for the originator; (4) the pharmacist notifies the prescriber in writing or electronic communication within 24 hours before the substitution; and (5) the patient must be informed and educated about biosimilar substitution.

Patients' Needs

Being able to rely on the efficacy and tolerability of biosimilars is of paramount importance for patients. As pointed out by the EULAR, concerns are frequently expressed by patients as to whether biosimilars are as effective as originators and whether their adverse effect profiles differ. Moreover, the lower price for biosimilars, compared with originators, has led to patient anxiety that the availability of lower-priced biosimilars may increase pressure on clinicians, health care professionals, and insurers to provide a biosimilar on the basis of cost alone. The UK National Rheumatoid Arthritis Society has issued a position paper that cautiously welcomes the introduction of biosimilars into the United Kingdom, but also highlights that it is important that biosimilars are prescribed purely for clinical reasons and not merely as a quick cost saving alternative to originators.⁸³ The position paper also alerts that switching patients for

nonmedical reasons could compromise health and long-term prognosis. In addition, it has to be considered that some patients are especially vulnerable to unwanted immune responses, such as pediatric and immunocompromised individuals, who may not necessarily be ideal candidates for switching to a biosimilar.⁸⁴

Given that biosimilars are more complex than generic small molecules, the need for patient education is greater and transparency of information is warranted; for this purpose, a clear specific nomenclature and full transparency of labeling may be helpful in increasing the confidence of both physicians and patients. The FDA has a page on its website that explains the basic principles about biosimilars to consumers; this page will need to be supplemented at the patient-practitioner level with more in-depth information and support, depending on the patient's disease state and economic and sociocultural factors.⁸⁵ Several patient organizations are also trying to assist patients in their understanding of biosimilars. As more evidence-based data on biosimilars becomes available, reliable codes of practice, recommendations, and points to consider would also be highly appreciated by patients to help build confidence and widen their understanding of biosimilar use.

Position Paper on Patients' Needs by the EULAR

The EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (SCPARE) has published a paper that incorporates some of the questions being asked and what is still needed to assist patients in their understanding of biosimilars in the context of making informed decisions.⁷⁵ This paper addresses the issues of switching, interchangeability, and substitution. Many patients consider that leaving open the possibility of switching, interchangeability, and substitution would introduce unacceptable uncertainties into the decision-making process. Thus, the EULAR SCPARE document calls for clear codes of practice, written in lay language and drawn up with the involvement of patients, so that patients can make fully informed decisions about whether to receive an originator or a biosimilar, to assess risk against benefit accurately, and to discuss the pros and cons with their health care team.

CONCLUSIONS

Current knowledge supports the following considerations on biosimilars. The development of biosimilars

is characterized by global harmonization, although several not fully answered questions remain regarding extrapolation of indications, switching or interchangeability, and tolerability. In patients with rheumatic diseases, analysis of tolerability and efficacy of biosimilars in clinical practice is an ongoing process that is being monitored. Several medical and patient associations have published position papers on biosimilars, requesting that tolerability, efficacy, and traceability should be carefully considered. Several position papers from medical and patient associations have highlighted the central role of physicians regarding the decision of which biopharmaceutical to use in treating patients; there is evidence in the literature that further long-term studies, including postmarketing surveillance, should be implemented that would allow physicians to gain greater confidence in biosimilars.

In conclusion, the shared opinion is that, although cost savings are highly desirable, the approval process for biosimilars needs to place tolerability and efficacy, supported by scientifically sound evidence, as the highest priorities. Importantly, academics should continue guiding the implementation of biosimilars into clinical practice, while continuing to search for improved agents and therapeutic approaches.

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CONFLICTS OF INTEREST

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