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OPINION ARTICLE

Biosimilars and Reference Biologics: Decisions on Biosimilar Interchangeability Require the Involvement of Dermatologists[☆]

Biosimilares y biológicos de referencia: la intercambiabilidad de los biosimilares requiere la participación del dermatólogo

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On September 13, 2013, the European Medicines Agency (EMA) approved the first biosimilar^a and treatment of moderate to severe psoriasis will be one of the indications. Undoubtedly this important news for dermatologists will have a major impact on prescribing patterns and management of patients with moderate to severe psoriasis.

On June 27, 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion and recommended that the EMA approve Inflectra (the applicant was Hospira UK) and Remsima (the applicant was Celltrion Healthcare Hungary Kft).¹ These biosimilars (CT-P13, Remsima) have already been approved in South Korea.² The 2 manufacturers (Celltrion and Hospira) have reached an agreement to market 8 biosimilars in the United States, Europe, Canada, Australia, and New Zealand. The active substance in both cases is infliximab, and both are biological medicinal products, similar to the reference product Remicade (infliximab), approved in the European Union since August 13, 1999. Published studies suggest that both products have a quality, safety, and efficacy profile similar to Remicade (infliximab). Thus the clinical trials PLANETRA³ and PLANETAS⁴ were able to show comparable efficacy to the innovator reference product infliximab in the treatment of

active rheumatoid arthritis (in combination with methotrexate) and ankylopoietic spondylitis, respectively, as well as similar pharmacokinetic, pharmacodynamic, safety, and immunogenicity parameters to those of the original infliximab (innovator infliximab according to the terminology of the CHMP). Of note is that the marketing authorization application for biosimilars includes all the approved indications for Remicade, thereby setting a precedent in terms of extrapolating the results between indications which, according to guidance, should be examined in separate trials. Although the reduction in price proposed by the sponsor, Celltrion, could be as large as 30% compared to the original product, it is unlikely that the 2 biosimilars will be available in most European countries before February 2015, when the patent extension awarded to Johnson & Johnson expires. Johnson & Johnson and its partner, Merck & Co, could take legal action if these products are marketed before then.⁵

What are the implications for everyday clinical practice of the approval of the first monoclonal biosimilar, with full extrapolation to all indications, in the European Union?

The introduction of biologic therapies for treating psoriasis has significantly improved the outcomes achievable with systemic treatments,⁶ and has in turn led to a change in therapeutic objectives.⁷ With some reference products approaching their patent expiry date, several manufacturers are developing follow-on versions or biosimilar products, which are expected to improve patient access to these drugs in health systems such as the Spanish one, reducing drug procurement costs and introducing competition to force down prices.

Biosimilars are biologic products very similar to the reference product in terms of quality, safety, and efficacy (EMA) or safety, purity, and potency (Food and Drug Administration [FDA]). Similarity is defined as no relevant

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^a Remsima R, from Egis, will be marketed under this trade name in several central and eastern European countries, and under the trade name Flammegis R in several members of the Commonwealth of Independent States.

difference in any of the parameters (quality/purity, safety, efficacy/potency). Demonstration of chemical similarity is not enough to demonstrate functional equivalence and comparative pharmacokinetic and pharmacodynamic trials should be conducted in healthy volunteers or patients, and there should be at least 1 clinical trial to demonstrate the equivalence of each formulation available.⁸

The variability of biological products depends not only on their amino acid sequence and primary structure, but also on posttranscriptional modifications such as glycosylation, methylation, oxidation, and deamination that may have an impact on tertiary structure (subunit folding) and quaternary structure (spatial configuration of the entire molecule). This in turn may lead to differences in affinity, selectivity, and functional, biological, and immunogenic activity compared to the reference biologic agent. Given that the manufacturers of biosimilars do not have access to the information on the production process of the patented reference product, it is very difficult to exactly replicate these post-transcriptional modifications, in contrast to small molecules (which will have exactly the same molecular structure as the reference product). The biosimilar is compared with the reference product by using validated analytical methods that enable the physical and chemical properties, biological activity, and purity and possible impurities to be determined. The directives currently in force allow for possible changes in the manufacturing process compared to the original, but the impact of these changes must be systematically assessed. Although biosimilars and their reference products are not identical, the same can be said for different batches of a reference biologic, given that the manufacturing processes are updated with each lifecycle. Changes might include switching the supplier of culture media, new purification methods, and even changes in the manufacturing facilities.⁹

Glycosylation patterns are extremely sensitive to minimal changes in the manufacturing process, and these probably lead to differences in the immunogenicity of the biological product. In the case of erythropoietins, the development of antibodies against the drug has given rise to cases of cross immunity with the physiological molecule, with potentially fatal outcomes.¹⁰ Such a situation is unlikely in the case of anticytokine antibodies. However, the development of antibodies against any biologic product may lead to blockade of its effect (neutralizing antibodies) or an increased clearance, in both cases reducing the clinical efficacy.¹¹ The nature of the antibody also contributes to the development of antibodies (the risk decreases according to whether the antibody is chimeric, humanized, or human) and induction regimens have been designed in part to achieve high serum concentrations and in part to induce tolerance to the development of these antibodies (intravenous administration contributes to this aim). The development of antibodies against the biologic agent appears to be more frequent in patients with autoimmune diseases, when administration is intermittent, and when background immunosuppressive medication (such as methotrexate) is not used. A recent metaanalysis in rheumatoid patients found that the presence of antibodies against the biologic product increases the risk of abandoning treatment and presenting with hypersensitivity reactions, whereas concomitant treatment with

antirheumatic disease-modifying drugs reduces the risk of such antibodies.¹² The clinical relevance of the loss of response, which determines adherence to a biologic and the need for switching to another agent, has contributed to the development of assays for detecting antidrug antibodies and for measuring serum concentrations of different biologics; these are currently available commercially and can be used in the clinical setting.¹³ The importance of these analytical techniques will no doubt increase when biosimilars are introduced. The extent to which they will be able to differentiate between biosimilars and their reference products remains to be seen.

The requirements for demonstrating similar clinical efficacy between a biosimilar and the reference biologic differ between the European Union (EU) and the United States. However, in both cases, at least 1 equivalence trial must be conducted with sufficient statistical power to demonstrate comparability of the 2 products in terms of efficacy and safety, that is, these products should be both noninferior and nonsuperior to the reference product.⁵ According to the EMA, immunogenicity should be assessed during the safety trial, whereas the FDA in the United States requires a comparative trial prior to marketing and another postmarketing trial. In both cases, a pharmacovigilance plan is required (and so it is essential to be able to distinguish the biosimilar, even when the drugs are prescribed interchangeably).

There has been plenty of discussion as to whether the findings of a clinical trial can be extrapolated to other indications, allowing the approval of a biosimilar for a therapeutic indication for which it has not been clinically assessed. Such an approach seems reasonable if the mechanisms of action are known and are common to both indications. When the mechanisms of action are different or not fully understood, or when the target organs or systems are different, separate clinical trials are probably required. In any case, any extrapolation should be made on a case-by-case basis and clearly highlighted as such in the Summary of Product Characteristics or Package Insert of the product.

A completely different situation is the interchangeability of biosimilar products and their originals and, therefore, the possible clinical or therapeutic equivalence. This is discussed in another article in the same issue of this journal. Any generic drug is interchangeable with the original, and the pharmacist can make the change without the prior authorization of the prescribing physician. The guidelines of the EMA make no reference to interchangeability of biosimilars, and the leave the corresponding decisions in hands of the health authorities of each member state of the European Union. In contrast, the legislation in the United States allows the FDA to determine which biosimilars can be interchanged without consulting the physician. The definitive guidance, however, has yet to be published. The interchangeability of biosimilars would hinder the tasks of pharmacovigilance; hospital pharmacists would have to follow the regulations in each country and bear in mind that the same international nonproprietary name (INN) in the case of biologics does not imply they can be automatically be used interchangeably.

The role of biosimilars in the treatment of psoriasis and other skin diseases would in part be determined by the assurances provided to the dermatologists by the regulatory requirements in the approval procedure, and to a

large extent by the pressures of the national and regional health authorities and hospital management to save money. Although a saving of 15% to 30% seems small compared to generics, biologics account for a high proportion of hospital drug expenditure. The decreased procurement cost of biosimilars will likely bring down the price of the original biologic products, particularly in situations where bidding is required. In addition, the manufacturers of the reference biologics are enhancing their biosimilar portfolio in an effort to diversify their business, minimize the price decreases, and avoid the subsequent impact on their market value.

In conclusion, the imminent arrival of biosimilars as therapeutic alternatives in dermatology should be welcomed if it allows savings to be made and more widespread access to treatment. The regulation introduced by the EMA in principle guarantees similarity between the approved biosimilars and the innovator product from the biochemical, pharmacokinetic, pharmacodynamic, immunogenic, and safety point of view for the indications in which trials have been performed. We should remember that the innovator biologics often end up becoming biosimilars of themselves (through changes in the manufacturing process) and in fact the regulatory framework for similarity in these cases is not so well defined as in the case of biosimilars. Although the good judgment of the experts at the EMA can be accepted a priori when they assess the extrapolation of indications, there are many gaps in our knowledge of the mechanism of action of different biologics, which can vary according to target organ. The clinician would feel much more assured with clinical trials that demonstrate the capacity to extrapolate the indication of the biosimilar to those of the original biologic when the target system/organ changes (musculoskeletal, digestive, or skin). Moreover, interchangeability brings with it issues with pharmacovigilance (if it is impossible to distinguish between biosimilars and originals) and ethics (can or should a treatment to which a patient is responding well be changed without the intervention of the prescribing physician and the consent of the patient?) In any case, it is imperative that the prescribing physician retains a say when making therapeutic decisions concerning biologics.

Conflicts of Interest

Dr. Lluís Puig has received honoraria as a consultant and speaker for Abbvie, Boehringer, Janssen, Merck-Serono, MSD, Novartis, and Pfizer. He has participated in clinical trials sponsored by Abbvie, Amgen, Janssen, Lilly, MSD, Novartis, Pfizer, and VBL.

References

1. European Medicines Agency recommends approval of first two monoclonal antibody biosimilars. Recommendation marks extension of biosimilar concept to new product-class [accessed July 12, 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001837.jsp%3Famp;mid=WC0b01ac058004d5c1
2. Puig L. Biosimilars in dermatology: Starting with infliximab. *Actas Dermosifiliogr.* 2013;104:175–80.
3. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. *Ann Rheum Dis.* 2013;72:1613–20.
4. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis.* 2013;72:1605–12.
5. New Drugs Online Report for infliximab biosimilar (CT-P13) [accessed July 12, 2013]. Available from: <http://www.ukmi.nhs.uk/applications/ndo/record.view.open.asp?newDrugID=5794>
6. Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, et al. Efficacy and safety of infliximab vs methotrexate in patients with moderate-to-severe plaque psoriasis: Results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol.* 2011;165:1109–17.
7. Puig L, Carrascosa JM, Carretero G, de la Cueva P, Fátima Lafuente-Urrez R, Belinchón I, et al., Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. Directrices españolas basadas en la evidencia para el tratamiento de la psoriasis con agentes biológicos, 2013. I. Consideraciones de eficacia y selección del tratamiento. *Actas Dermosifiliogr.* 2013.
8. Tsiftoglou AS, Ruiz S, Schneider CK. Development and regulation of biosimilars: Current status and future challenges. *BioDrugs.* 2013;27:203–11.
9. Schneider CK. Biosimilars in rheumatology: The wind of change. *Ann Rheum Dis.* 2013;72:315–8.
10. Roger SD. Biosimilars: Current status and future directions. *Expert Opin Biol Ther.* 2010;10:1011–8.
11. Garcès S, Demengeot J, Benito-García E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. *Ann Rheum Dis.* 2012.
12. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated inflammatory conditions: Systematic review and meta-analysis. *JAMA Intern Med.* 2013;24:1–13.
13. Dörner T, Strand V, Castañeda-Hernández G, Ferraccioli G, Isaacs JD, Kvien TK, et al. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis.* 2013;72:322–8.