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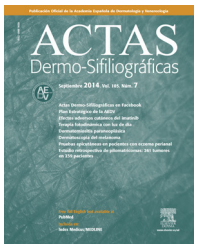

OPINION ARTICLE

The Use of Biosimilar Drugs in Psoriasis: A Position Paper☆

Fármacos biosimilares en psoriasis: informe de posicionamiento

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Background

- The development of biologic therapy has substantially improved the treatment of psoriasis and psoriatic arthritis. At the same time, the elevated cost of biologics has prompted debate on the economic sustainability of the public health system.
- As patents expire for biologics, business interests and the high capacity of today's biotechnology industry have encouraged laboratories to develop new drugs—called biosimilars—that have effects that resemble those of their reference biologics. In principle, these biosimilars are equal to their reference biologics in efficacy and safety, but they cost less.
- This attractive theoretical situation, in combination with the influence of parties interested in the business of biologic therapy and the need to curtail public health system spending on this type of drug, has logically fueled a certain amount of debate about biosimilars. Physicians, patients, and the pharmaceutical industry have all taken part. A similar debate took place years ago when generic drugs were introduced.
- With 2 biosimilars for treating psoriasis and psoriatic arthritis already approved by the European Medicines Agency (EMA) and about to enter the market, this seemed to us to be a good time for dermatologists to state our position on several aspects related to these new drugs.

Considerations

Definition

A biosimilar is a biotechnological medicinal product that contains the same active substance as a reference biologic and is prescribed for treating the same disease at the same dose and route of administration. As their name indicates, biosimilars are highly similar to reference biologics, but because of differences in manufacturing processes they are not identical.

Approval

The European Union (EU) approves biosimilars and authorizes their sale following a centralized procedure that upholds the same quality standards that apply to reference biologics and meets the specific requirements and regulations imposed by the EMA regarding manufacturing quality controls.

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Biosimilarity

Biosimilarity can be demonstrated by 2 basic conditions: 1) that the biosimilar drug's structure is highly analogous to that of the reference biologic, a condition that requires the new drug to be characterized through exhaustive analyses; and 2) that the biosimilar's quality, safety, efficacy and immunogenicity profile is similar to the reference biologic's, a condition that requires the completion of properly designed clinical trials. Changes in the reference biologic's manufacturing process can also cause small variations from the original drug and may also make it necessary to run trials to demonstrate comparability in the context of a particular use, followed by extrapolation to other uses.

Indications

A biosimilar has the same indication as its reference biologic. The use we are concerned with in this paper is the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, are intolerant to, or have a contraindication for other systemic therapies, including cyclosporine, methotrexate, or psoralen plus UV-A therapy. The clinical use of a biosimilar is guided by the same criteria that apply to its reference biologic.

Efficacy

EMA directives state that a biosimilar's clinical efficacy must be established by a randomized double-blind clinical trial in a population representative of patients with the condition the reference biologic is approved for. The trial must have sufficient power to detect differences between the biosimilar and the biologic. For the 2 infliximab biosimilars recently approved by the EMA (corresponding to CT-P13, developed by Celltrion), approval was supported by data from clinical trials in patients with rheumatoid arthritis and ankylosing spondylitis, but not specifically in patients with psoriasis.

Extrapolation

Biosimilars can be approved for all or some of the indications the reference biologic is approved for, but not for more indications. Even though the EMA's recent approval of the 2 infliximab biosimilars is based on efficacy and safety results in patients with rheumatoid arthritis and ankylosing spondylitis, the agency's European Public Assessment Report lists the same indications approved for infliximab. South Korea, Colombia, Turkey, and Japan have done likewise, whereas the health authorities in Canada have chosen not to include Crohn disease or ulcerative colitis among the extrapolated indications. A trial (NCT02096861) is under way to demonstrate the noninferiority of CT-P13 and evaluate its efficacy in 214 patients with active Crohn disease.

Safety

The dossier a manufacturer presents to the EMA when applying for approval of a biosimilar must contain data that show that there are no substantial differences between the biosimilar and its reference biologic. Once an approved biosimilar is on the market, it must submit to a pharmacovigilance program that matches in rigor the program set up for the reference biologic. To that end, each drug must be traceable and identifiable at all times so that the possible adverse effects that might be attributed to it can be registered. Therefore, so that a biosimilar given to a patient can be clearly identified, the label should include the common name (international nonproprietary name), commercial name, and/or the manufacturer's name.

Interchangeability and Switchability

The EU does not address the issues of interchangeability or switchability between a reference biologic and a biosimilar. This aspect is left to the judgment of each member state. Regulations in Spain leave the decision to the physician: whereas a pharmacist may switch one manufacturer's generic drug for another's, a biosimilar may not be automatically substituted for its reference biologic. The prescribing physician is responsible for the decision.

Conclusions

1. The Spanish Academy of Dermatology and Venereology (AEDV) celebrates the incorporation of biosimilars into the treatment regimens for psoriasis and psoriatic arthritis. Thanks to these new drugs, the high cost of biologic therapy is likely to decrease, reinforcing the sustainability of the public health system, a goal the AEDV supports. However, the use of biosimilars should not imply a reduction in therapeutic efficacy, patient safety, or the prescriber's freedom of choice.
2. Regarding innovation, biosimilars do not seem to offer advantages over reference biologics, but they do represent savings. Nevertheless, decisions about which drug to prescribe should not be based on economic considerations alone, but rather on scientific evidence. We therefore recommend that dermatologists, pharmacists, managers, and other stakeholders be involved in decisions about how biosimilars are introduced into our health care system.
3. The AEDV calls for psoriasis and psoriatic arthritis patients to be included in clinical trials of these new drugs to the degree possible. The purpose of such inclusion would be to obtain direct information about efficacy and safety, so that we do not have to extrapolate from findings for other disease contexts. Extrapolations are made to other diseases related to the ones reflected in trials, but these contexts are not necessarily identical with respect to how the biosimilar drug behaves (mechanism of action, dosage, or in possible combinations with other treatments). If possible, we need clinical trials for indications in which the difference in efficacy between the drug and placebo is greatest: such is the case in psoriasis in comparison to rheumatoid arthritis.
4. Once the biosimilar is on the market, both the new drug and its reference biologic should become available to prescribing dermatologists in hospitals. The physician will take responsibility for choosing to prescribe a

biosimilar, and the choice must be guided by the same criteria applied to the clinical use of the biologic.

5. We believe that the decision to prescribe a biosimilar should be assessed on a case-by-case basis and that the patient must agree with the choice. Switching from a biologic to a biosimilar should also be decided by the physician with the patient's consent.
6. Given that it is impossible to absolutely establish that a biosimilar and a reference biologic are identical, even slight differences between them might have clinical consequences. Therefore, information about the true efficacy and safety of biosimilars in the treatment of psoriasis and psoriatic arthritis must be confirmed afterwards, once biosimilars are on the market and in use and once the relevant pharmacovigilance data are being registered.
7. Biosimilars on the market should come with patient and prescriber information that is clear and precise, so that prescriber and patient can make proper decisions about the acceptability of these drugs. Given the doubts that this new concept of biosimilarity may arouse among both dermatologists and users, we must take steps to inform and teach those concerned. Ideally information should reflect consensus formed before these new drugs are used routinely. The AEDV is willing to collaborate with other parties to achieve that goal.
8. The opinions we hold about biosimilars today may change in the light of the experience that will come after commercialization and/or the publication of new trails.

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Conflicts of Interest

Dr G. Carretero Hernández has participated in clinical trials and postapproval studies sponsored or funded by Abbvie, Celgene, Janssen, Lilly, MSD, Novartis, and Pfizer. He has received consultancy or speaker's fees from Abbvie, Celgene, Janssen, MSD, Novartis, Pfizer, and Leo.

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