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NOVELTIES IN DERMATOLOGY

Biosimilars in Dermatology: Current Situation (Part II)☆

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Abstract The first biosimilar version of a biologic agent used to treat psoriasis (infliximab) entered the Spanish market on February 16 of this year, and more biosimilars can be expected to follow in the coming months and years. Logically, this new situation will have economic repercussions and alter prescribing patterns among dermatologists. In this second part of the review, we will look at several somewhat contentious issues, such as the extrapolation of indications, interchangeability, and automatic substitution. We will also review the biosimilars with indications for psoriasis currently in the clinical development pipeline and assess their potential to offer comparable efficacy and safety to the reference product while contributing to the sustainability of the public health care system.
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Biosimilares en dermatología. Situación actual (parte II)

Resumen El 16 de febrero de este año se han comercializado en España los primeros biosimilares de un tratamiento biológico para la psoriasis (infliximab), y en los próximos meses y años está prevista la incorporación de otros biosimilares, con un previsible impacto económico y en los hábitos de prescripción dermatológicos. En esta parte de la revisión se abordan aspectos objeto de cierta controversia, como la extrapolación de indicaciones, la intercambiabilidad y sustitución automática, los biosimilares en fase clínica de desarrollo con indicaciones que incluyen la psoriasis, y unas consideraciones finales sobre el potencial de estos fármacos para proporcionar unas alternativas terapéuticas de eficacia y seguridad comparables a las de sus productos de referencia, contribuyendo a la sostenibilidad del sistema sanitario público.
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Extrapolation to Other Indications

In September 2013, the European Medicines Agency (EMA) approved CT-P13, the first biosimilar of the monoclonal antibody infliximab. This biosimilar antibody was developed by Celltrion and launched in Spain on February 16, 2015 (after the patent for Remicade had expired) under the names of Remsima (Celltrion Healthcare Hungary Kft, distributed by Kern Pharma) and Inflectra (Hospira UK Ltd). This product is approved for all of Remicade's indications (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn disease, ulcerative colitis, and plaque psoriasis, and Crohn disease and ulcerative colitis in children), although the comparative clinical trials were only conducted in patients with rheumatoid arthritis and ankylosing spondilytis.[1] The Canadian medicines agency (Health Canada), the EMA, and the Food and Drug Administration (FDA) are the main agencies to have taken a stance on the regulatory considerations for permitting extrapolation of indications in biosimilar medicines. The EMA considered the results of the trials for patients with rheumatoid arthritis to be sufficiently sensitive to permit extrapolation to all other indications. Health Canada, in contrast, has not approved extrapolation for indications in inflammatory bowel disease because of differences in the in vitro antibody-dependent cytotoxicity assays, potential differences in the mechanism of action of the agent in these indications, and the lack of clinical trials.[2]

When interpreting the comparative studies of this first biosimilar monoclonal antibody to be approved, certain considerations need to be addressed[3–5]:

1. In comparative clinical trials in patients with rheumatoid arthritis and ankylosing spondylitis, participants are allowed to use methotrexate. Methotrexate is a drug that is indicated in its own right for the treatment of rheumatoid arthritis. It also enhances the action of infliximab and other tumor necrosis factor inhibitors (anti-TNF) by reducing immunogenicity. In rheumatoid arthritis, combined use is common. However, in other indications such as psoriatic arthritis, Crohn disease, ulcerative colitis, and plaque psoriasis, anti-TNF agents are usually used in monotherapy or in combination with other immunosuppressive drugs. Rheumatoid arthritis may therefore not be the most sensitive disease for measuring significant differences between drugs.
2. With regard to the mechanism of action, antigen neutralization only requires binding to the Fab fraction of immunoglobulin, whereas antigen-dependent cell cytotoxicity and induction of apoptosis require the participation of the Fab and Fc fractions of the monoclonal antibody, acting on the appropriate receptors of the effector cell. The first of the above mechanisms of action appears to be key in rheumatoid arthritis, whereas the second is more important in inflammatory bowel disease.
3. With regard to immunogenicity, the FDA recommends using the most sensitive population to detect it, that is, the one at greatest risk of developing an immune response to the drug through formation of antidrug antibodies. This process is closely correlated with side effects, which are mainly acute and include events such as infusion-related reactions in the case of infliximab. In this case, the ankylosing spondylitis population is perhaps not the most sensitive because these patients have been shown to develop antidrug antibodies less frequently than patients with plaque psoriasis, Crohn disease, and ulcerative colitis.
4. In terms of safety, comparative clinical studies in patients with rheumatoid arthritis and ankylosing spondylitis did not include pediatric patients or patients who were receiving immunosuppressants other than methotrexate, and so extrapolation in these cases would require extreme caution.
5. From the pharmacokinetic point of view, there are also differences in the clearance rate according to the patients' underlying disease, as clearance ie 45% higher in patients with Crohn disease than in those with rheumatoid arthritis. This clearance rate may also be affected by the use of concomitant medication and development of antidrug antibodies.

Some scientific societies have started to pronounce against extrapolation of indications, or in favor of doing so provided that effective and safe clinical use is guaranteed, supported by appropriate postmarketing pharmacovigilance

systems for the product.[5,6] When the target organ (musculoskeletal system, digestive tract, or skin) differs and there may be differences in terms of mechanism of action, it is recommended to conduct independent clinical trials to confirm the extrapolation, and evaluate each case on an individual basis.[7] Although absolute certainty is impossible to achieve, the degree of uncertainty is less for biosimilars than for the innovative product. In fact, biosimilars have been on the European market for several years, and their performance has been as expected in all approved indications, including the extrapolated ones.[8]

Traceability

The EMA, in collaboration with the member states of the European Union (EU), is obliged to draw up, update, and publish in the public domain the list of drugs that are subject to additional follow-up, that is, medicinal products authorized in the EU that contain a new active substance which, on 1 January 2011, was not contained in any previously authorized medicinal product as well as any biological medicinal product authorized thenceforth (Articles 17 and 23 of EC Regulation 1235/2010). As regards pharmacovigilance and notification of adverse events, Directive 2010/84/EU amends Article 102 of Directive 2001/83/EU, requiring member states to enact appropriate measures for identifying any prescribed biologic drug that is dispensed or sold in their territory and to record the trade name and batch number in the event that an adverse event is reported.

In any case, traceability will be possible only through large pharmacovigilance databases and through specific studies and registries. The supply chain shall be identified and it shall be possible to trace the drug in the event of adverse reactions occurring during treatment.[9]

Interchangeability and Substitution

The requirements for interchangeability have not been completely defined.[10] In the United States, the Biologics Price Competition and Innovation (BPCI) Act requires the following conditions for a product to be considered interchangeable[11]: the biologic has to be biosimilar to the reference drug; the biosimilar can be expected to give the same clinical result as the reference product in a given patient; and, for a biosimilar administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between products should not be greater than the use of the reference drug without such alternation or switch.

According to many experts, substitution (by the pharmacist, without approval of the prescriber) may be harmful for the patient, hinder pharmacovigilance, and reduce the traceability of the biosimilar.[12]

The regulations vary according to each region. In the United States, the FDA has established that a biosimilar that complies with the requirements of the BPCI act can automatically be substituted. In Europe, the EMA delegates the responsibility for this decision to the member states. For the time being, few member states have clearly defined their position, and the regulatory requirement in Spain is confusing and pending development.

The scientific societies of the different specialties that use biologics are taking positions on the question of substitution, among other issues. In a recent position statement, the Spanish Society of Rheumatology concluded that "biologic agents are not generic versions of their reference product and so are not automatically interchangeable. The substitution of a biologic agent with a biosimilar is a medical act that should be performed exclusively by the prescribing physician with the consent of the patient."[13] For its part, the Spanish Society for Digestive Diseases, along with the Spanish Society of Pharmacology, in an article describing their institutional stance, concludes that substituting a biosimilar for a biologic reference agent is an unacceptable practice.[14] The organizations of patients with chronic diseases (whose members number more than 5 million) have also pronounced in this respect, and are against interchangeability and substitution of a biologic with a biosimilar.[15]

Current Situation in Dermatology and Future Prospects

The approval of an infliximab biosimilar by the EMA has paved the way for other biosimilars of original biologics whose patent is close to expiry.[16]

Currently, clinical trials are ongoing with biosimilars of etanercept and adalimumab, both in psoriasis and rheumatoid arthritis. In the case of psoriasis, the trial of the etanercept biosimilar GP2015 (Sandoz/Hexal, trial identification NCT01891864), with 546 patients, is expected to finish in April of 2015. There are also 2 ongoing trials of biosimilars of adalimumab (whose patent expires in 2018): APB 501 by Amgen, with 350 patients (NCT01970488) with expected end date of June 2015, and GP2017 by Sandoz/Hexal, with 448 patients (NCT02016105), expected to finish in August 2015.

Of note, not all the drugs that have been marketed as biosimilars in some countries comply with the European legislation. For example, etanercept has 2 biosimilar products produced in China. One of these, despite similar affinity and bioactivity to the original, has a different molecular mass, amino acid composition, and glycosylation pattern, thus not meeting the EU requirements for recognition as a biosimilar.[17] Strictly speaking, this agent can only be considered as an intended copy. Regulatory harmonization and development of pharmacovigilance systems are necessary in countries with regulations less stringent than those of the EMA.[18]

Final Considerations

The biologics market looms large but also risky. Only large companies appear able to enter the sector and navigate regulatory issues. Part of the initial investment requires acquisition of the original product for the clinical trials, and also implementation of the pharmacovigilance measures demanded by the regulatory authorities. There is also the risk of additional costs arising from extension of the original patent protection and intellectual property litigation, which not may only delay the launch of stockpiled product but also cause losses if the expiry date is exceeded. Nevertheless, the manufacturing process for biosimilars is

less expensive than that of the original, since the technology used is more up to date. In addition, biosimilars require fewer clinical trials than the original for approval in different indications. Cost is also an important driver for the healthcare systems: biosimilars are expected to reduce procurement costs not only because the biosimilar itself is less expensive but because the price of the corresponding original may decrease, either through market pressures or as a result of regulatory impositions.

Progress will not be easy for biosimilars, as they require appropriate distribution and supply logistics, as well as a special pharmacovigilance plan, with particular focus on potentially serious adverse effects. They will also need to overcome the initial reticence of physicians to use a product that has not been tested in specific clinical trials for the indication, and without the years of experience that reference products offer. Automatic substitution of the original product with a biosimilar is not feasible in the Spanish system without a medical prescription. In addition, if the difference in recommended retail price, the only initial advantage of the biosimilars, is evened out, it will be hard to convince the physicians to turn to a biosimilar as a first option.

In any case, time will tell whether biosimilars are the solution to ensure access for a broad sector of the population to certain treatments which would otherwise be too expensive for health systems or whether the reference products will continue to be used due to lower costs resulting from competition with biosimilars.

Conflicts of Interest

L. Puig has received consultant fees and/or speakers fees from Abbvie, Amgen, Boehringer-Ingelheim, Celgene, Janssen, Leo-Pharma, Lilly, MSD, Merck-Serono, Novartis, and Pfizer, and has participated in clinical trials sponsored by Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer, and VBL. G. Carretero has participated in clinical trials and post-marketing studies sponsored or funded by Abbvie, Celgene, Janssen, Lilly, MSD, Novartis, and Pfizer. He has received speaker or consultant fees from Abbvie, Celgene, Janssen, MSD, Novartis, Pfizer, and Leo Pharma. E. Daudén has carried out the following activities: advisory board member, consultant, grant recipient, research support, participation in clinical trials, paid talks with the following pharmaceutical companies: Abbvie/Abbott, Amgen, Janssen-Cilag, Leo Pharma, MSD, Pfizer, Novartis, Celgene, and Lilly. S.E. Marrón has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, and Pfizer. He has participated in clinical trials sponsored by Amgen and VBL. A. Martorell has received consultant fees and/or speaker fees, and/or has participated in clinical trials sponsored by Novartis, Abbvie, Janssen, Galderma, and Pfizer. B. Pérez-Suárez has received consultant fees and/or speaker fees, and has participated in clinical trials sponsored by Almirall, Abbvie, Janssen, and Pfizer. C. Rodríguez-Cerdeira has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, and Almirall. R. Ruiz-Villaverde has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, Novartis, and Pfizer. J.L. Sánchez-Carazo has received consultant, speaker, and advisory board member fees from Abbvie, Amgen, Celgene, Janssen, Lilly, MSD, Merck-Serono, Novartis, and Pfizer, and has participated in clinical trials sponsored by Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer, and VBL. M. Velasco has participated in clinical trials sponsored by Pfizer España and has received consultant and speaker fees from Abbvie, Merck, Janssen, and Pfizer. The remaining authors declare that they have no conflicts of interest.

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