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Editorial

[Translated article] A decade of experience with biosimilar monoclonal antibodies

Una década de experiencia con biosimilares de anticuerpos monoclonales

The entry of infliximab –the first biosimilar monoclonal antibody– into the market ten years ago (February 2015) was a hallmark in the history of biosimilars in our country.[1] At that time, biosimilar antibodies had been on the Spanish market for nine years, following the authorization of the first biosimilar (human growth hormone) in 2006. However, the impact generated by the few available biosimilar drugs, based on relatively simple biological molecules and primarily used for supportive care, had been minimal.

Then, the challenge arose to convince healthcare professionals and patients of the validity of the complex protein biosimilars known as monoclonal antibodies. These artificial molecules feature large, complex, three-dimensional structures inducing glycosylations and a host of biochemical processes[2], which raised some concerns regarding the use of infliximab biosimilars. Infliximab played a central role in the treatment of chronic, severe and relatively prevalent diseases such as arthritis, psoriasis or inflammatory bowel disease (IBD).

The European Medicines Agency (EMA) developed specific guidelines for the evaluation of biosimilar drugs containing monoclonal antibodies.[3] The EMA initially approved their use for specific diseases based on evidence of efficacy and safety, and subsequently extended the authorization to IBD through extrapolation from the original data. The lack of confirmatory clinical trials supporting the efficacy and safety of monoclonal antibodies in ulcerative colitis and Crohn's disease was a major barrier to the adoption of these treatments by specialists.

This marked the beginning of a long-term effort to raise awareness among physicians and patients that the comparability exercise had been consistently applied throughout all stages. The concept of extrapolation of indications –already in use for originator drugs– progressively entered the mainstream discourse in scientific forums concerning biosimilar drugs. Indeed, the Spanish Agency for Medicines and Medical Devices organized a monographic session focused on this concept[4], with a clear educational intent.

In their position statements, the scientific societies and patient associations relevant to these conditions reflected a cautious attitude toward the adoption of these therapies. They also urged the different Spanish autonomous communities to update their policies as new evidence supporting the efficacy and safety of these medications became available.[5] Concerns were also voiced about initiating these therapies in treatment-naïve patients, and more notably, about switching patients from originator drugs to an alternative biosimilar drug. The person who would bear responsibility for switching treatments was also a matter of debate. For years, the issues of treatment switch, substitution, and interchangeability, and the legal responsibilities they entail stood at the forefront of discussions concerning these therapies.

In this context, the Spanish Society of Hospital Pharmacy (SEFH) became aware that building confidence in these agents was essential for their orderly adoption in routine practice. For this purpose, in 2017, the SEFH published a position statement on biosimilar drugs[6] that underlined *"the guarantees inherent to the rigorous authorization process carried out by the EMA"*, as well as the importance of "*consensus among stakeholders*" in addressing the issue of interchangeability.

Since then, it took five years for the EMA and the Heads of Medicines' Agencies to issue a position statement on the interchangeability of biosimilar medicines.[7] From a scientific point of view, they considered that biosimilar medicines are interchangeable with their reference product (or vice versa) or with another biosimilar. However, responsibility for decisions on the implementation of switching (when prescribing) and substitution (when dispensing) should fall on each member state. This delay in issuing a statement was not intentional, but a clear example of the importance of gathering solid evidence before formulating a statement regarding a particular drug therapy, which requires time.

On another note, it would be naïve to believe that initial reluctance stemmed only from understandable doubts and caution regarding the arrival of something new. For the first time, biosimilar drugs are positioned in the segment of blockbusters. In 2014, adalimumab and infliximab ranked first and second among the top 15 hospital medicines accounting for the highest pharmaceutical hospital spending, representing €280 and €170 million in costs (calculated at ex-factory prices).[8]

The entry of infliximab and adalimumab biosimilars in 2015 and 2018, respectively, generated competitive dynamics, ultimately resulting in a long-awaited decrease in their pricing. Biosimilar drugs have also been developed for other monoclonal antibodies included in the list of medicines accounting for the highest hospital drug expenditure regularly published by the Spanish Ministry of Health: in oncology, rituximab (2017), trastuzumab (2018) and bevacizumab (2020). Notably, biosimilar drugs have been progressively developed for ophthalmological (ranibizumab, 2022), neurological (natalizumab, 2024) and rare diseases (eculizumab, 2023). Of note, with the recent authorization of ustekinumab biosimilars (2024), immune-mediated diseases (arthritis, psoriasis, IBD, to name a few) have become the main field of application of biosimilars.

Biosimilars have overcome initial reluctance and perceptions to progressively gain ground in the market. In the case of infliximab, its

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biosimilars have reached a market share of 90% in seven years.[9] A comparable trend is observed in other biosimilars indicated for chronic diseases; however, for these biosimilars to acquire a market share, it is required that patients receiving the originator drug switch to the biosimilar. This growth has been considerably more substantial in biosimilars indicated for acute disease. Such is the case of bevacizumab, which has conquered 90% of the market share in only three years.[9]

The progressive adoption of biosimilars has resulted in significant cost savings for the National Health System, primarily due to increased market competition, which has led to price reductions of over 50% in many public procurement processes.[10] A budget impact analysis of biosimilars within the National Health System[10] estimated the savings generated by market competition of infliximab at 948 million euros between 2015 and 2022, and 972 million euros for adalimumab between 2018 and 2022. These are the drugs that, with the shortest time on the market, have contributed the most to the savings derived from biosimilars.

Beyond cost savings, biosimilars are enabling broader and earlier access to new therapies. In 2021, the National Institute for Care Excellence, prompted by the introduction of biosimilars in the market and the reductions in prices, expanded the use of several anti-TNFs to patients with moderate rheumatoid arthritis[11], which had previously been restricted to those with severe rheumatoid arthritis. The Institute also estimated that over 25,000 new patients could benefit from this change in their guidelines. In Spain, the use of infliximab, adalimumab and etanercept has increased by 1.25 times between 2017 and 2020 since the advent of biosimilars, which suggests a "democratization" in their use. The broader use of biosimilars may involve that patients with comparable disease severity are gaining earlier access to a first-line biologic therapy.

In 2023, the SEFH published the results of a retrospective observational study performed in 15 hospitals in nine autonomous communities involving patients with immune-mediated inflammatory diseases. This study uncovered that the introduction of anti-TNF biosimilars has contributed to a 1.6-year (19 months) reduction in the waiting time to access first-line biologic therapy.[12]

In the past, due to their high cost, access to biologic therapies was often restricted to patients with refractory or severely advanced disease. However, a growing body of evidence indicates that biosimilars facilitate earlier initiation of treatment, leading to enhanced clinical outcomes[13] and an improved quality of life. In this regard, one of the main challenges for the country is to establish usage guidelines that ensure equitable access to therapies, as is the case in other European countries.[14]

Likewise, it is also important to acknowledge the role of biology in incremental innovation. Although *biosimilar* and *innovation* are often considered opposing terms –if not antonyms–, there are some iconic examples illustrating how innovation in mature pharmaceuticals has had a meaningful impact not only on patient outcomes but also on healthcare management. For example, in 2020, the European Commission authorized the first subcutaneous formulation of infliximab, whose originator was only available for intravenous administration. This formulation, which enables patient self-administration, supported the continuation of treatment for individuals with IBD during the SARS-CoV-2 pandemic and demonstrated substantial advantages in terms of therapeutic flexibility and reduced burden on hospital services.[15]

Ten years later, the entry of the infliximab biosimilar into the market not only served as a catalyst for learning about biosimilars at all levels but also acted as a key enabler for the subsequent introduction of other complex protein biosimilars (rituximab, trastuzumab, adalimumab). Current usage figures are the result of the shared effort of the scientific community, regulatory agencies and healthcare professionals to successfully optimize the use of public healthcare resources and improve the quality of life of thousands of patients.

Biosimilars not only contribute to cost saving, which is not trivial in a public healthcare system constantly overstressed by rising pharmaceutical spending, but also they represent more alternatives and more options, resulting in enhanced patient safety. Biosimilars also constitute a form of incremental innovation. Commemorating this anniversary ultimately serves as a recognition of the collective effort to transform uncertainty into certainty and lack of knowledge into evidence.

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Isabel Río Álvarez: Conceptualization, Writing – original draft. **Encarnación Cruz Martos:** Conceptualization, Writing – review & editing.

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Conflict of interest

Isabel Río Álvarez and Encarnación Cruz Martos hold positions within Asociación Española de Medicamentos Biosimilares (BioSim) (Spanish Association of Biosimilars).

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