BRIEF COMMUNICATION

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Are we ready for multiple switches between reference products and biosimilars?

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HIGHLIGHTS

- The most crucial benefit of biosimilars is that they bring more significant cost reduction and increase access to advanced therapies.
- For this to occur, it is imperative not only to use biosimilars in naïve patients but also to switch to biosimilars in those patients who have started therapy with reference biologics.
- So far, studies have demonstrated effectiveness and safety of single switch between a reference product and a biosimilar.
- The purpose of this manuscript is to discuss whether scientific evidence is enough to support multiple switches of biologics and biosimilars in IBD patients.

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ABSTRACT – Inflammatory bowel diseases (IBD) currently impose an immense social and economic burden on society in terms of both direct and indirect healthcare costs. Their incurable and progressive nature results in an unavoidable lifetime expense. The introduction of infliximab more than two decades ago had revolutionized IBD treatment. Nowadays, while biologic drugs comprise various vital therapeutic options for patients, they can be associated to significant costs to healthcare systems. The most crucial benefit of biosimilars is that they bring more significant cost reduction and increase access to advanced therapies. They also allow the treatment of newly diagnosed patients and dose optimization for those who need it. There is an inverse relationship between price and demand for treatment with biologics. For a more significant reduction in cost to be possible, greater use of biosimilars is necessary. For this to occur, it is imperative not only to use biosimilars in naïve patients but also to switch to biosimilars in those patients who have started therapy with reference biologics. At present, randomized and observational studies have demonstrated effectiveness and safety results in recommending a single switch between a reference product and a biosimilar, and vice versa. The purpose of this manuscript is to review the literature and discuss whether scientific evidence is enough to support multiple switches of biologics and biosimilars in IBD patients.

Keywords: biosimilar, inflammatory bowel disease, infliximab, SB2, CT-P13.

It is probable that after the approval of the first biosimilar of a monoclonal antibody (CT-P13) by the European Agency of Medicine (EMA) in 2013, a new revolution of immune-mediated diseases' treatment would take place[1,2]. The rationale for this prediction was that introducing a biosimilar would offer a 20-30% price reduction compared to biologic reference. Moreover, market competition would reduce the pricing of references products. Then, cheaper biosimilars combined with market competition, even with a reduction in the biologic reference price, would increase access to treatment[1-3]. The purpose of all biosimilars is purely economic. They came to stay.

Before CT-P13, a systematic review of economic studies on biologics used to treat Crohn's disease (CD) concluded that long-term use of biologics might lead to higher cost as compared to its benefit, whereas less than optimal use (just induction or induction followed by episodic treatment) did result in poor clinical outcomes, despite lower costs[4]. Five years after CT-P13 arrived on the market, other studies failed to show the cost-effectiveness of using a biological in IBD management. While biologic agents helped to improve outcomes (QALYs and remission rates), they incurred high costs and were not cost-effective, particularly for use as maintenance therapy[5].

A decade has passed since the first monoclonal antibody biosimilar reached the market. What is the current scenario for biosimilars in IBD? So far, EMA has approved several different biosimilars of three anti-TNF agents. Two monoclonal antibody anti-TNF biosimilar drugs used in IBD and other indications such as Rheumatoid Arthritis, Psoriatic Arthritis, Juvenile Arthritis, Ankylosing Spondylitis, Psoriasis, and Hidradenitis Suppurativa: infliximab (2013) and adalimumab (2017). Moreover, EMA approved a fusion protein biosimilar etanercept, which is not indicated for IBD. The cumulative patient treatment days for EMA-approved biosimilars have doubled every 1.5 years, with the total clinical experience with biosimilars currently being 5.8 billion patient treatment days (as of September 2023)[5,6]. The opposite occurs in the United States (US). Despite price reduction, infliximab biosimilars still have much lower use rates than other biosimilars such as filgrastim, bevacizumab, and trastuzumab, ranging from 60% to 80% a year[7]. The systems in place in European Union (UE) countries are promoting the improved use of biosimilars. This contrasts with what is happening in the US, where, out of the $126 billion spent on biologics in 2018, only approximately 2% was spent on biosimilars[7]. The reason for this discrepancy between the EU and the US is that, in America, there is a continued lack of physician's familiarity with use and trust in biosimilars. As a result, physicians may be hesitant to switch patients to biosimilars. The Food and Drug Administration (FDA) released final guidance on therapeutic interchangeability between originator biologics and biosimilars. Furthermore, the last update (March 2024) of the FDA's Purple Book included three adalimumab interchangeable biosimilars (adalimumab afzb, adalimumab atto, and adalimumab ryvk)[8]. Shortly, with a switch at the pharmacy level (automatic substitution), single switch, cross switch, and even multiple switches will often occur in the US.

Biosimilars have come onto the market to increase the number of treatment options available, increasing competition. This can reduce the significant price of reference biological products, saving money for public and private healthcare systems[1,2,3,5,9]. From the point of view of a healthcare professional treating IBD, the most important benefit of biosimilars is to bring greater cost reduction and significantly increase in access to advanced therapies, in addition to allowing the treatment of newly diagnosed patients and optimizing therapy for those who need it. There is an inverse relationship between biologic price (reference or biosimilars) and the demand for treatment. For a greater reduction in cost to be possible, greater use of biosimilars is necessary. For this to occur, it is imperative not only to use biosimilars in naïve patients, but also to switch to biosimilars in those patients who have started reference biologics. Furthermore, it is important to allow the patient to receive the lowest-cost medicine and switch from reference to biosimilars back and forth, switching between biosimilars as often as necessary. However, for this bold strategy to be possible, it is not exclusively necessary for the scientific community to accept it. In fact, physicians and patients should agree. Last year, a survey answered by IBD specialists provided insights regarding practical management, beliefs, and knowledge surrounding biosimilars[10]. The 17 specialists from

13 countries have come to 2 important statements: 1. The switch from an originator drug to a biosimilar is effective and safe (agreement 100%); 2. Multiple switches from one biosimilar to another are feasible in case of unavailability (agreement 100%)[10]. Recently, a systematic review of the literature analyzed the physicians' perceptions of the uptake of biosimilars[11]. The proportion of physicians willing to switch from an originator to a biosimilar was 51% or less, except in a single study in which the percentage was 91%. However, gastroenterologists (95%, with no concerns) seemed to be the most confident specialists in regards to switching, followed by dermatologists (78%), diabetologists (69%) and, notably, rheumatologists (53%) [11]. Education and national recommendations and policies for the switching and substituting biological originators are needed to support the uptake of biosimilars[3,9,11]. Currently, the EU and other countries, except for the US, have favorable scenarios for switching. In September 2022, EMA published a joint statement confirming that biosimilars approved in the EU are interchangeable with their reference products or with an equivalent biosimilar. It has brought more clarity for healthcare professionals and thus allows more patients to access biological therapies across the EU. Furthermore, as time passes by after biosimilar approval, the effectiveness and safety of a single non-medical switch (NMS), defined as switching in stable patients who are generally doing well with their current therapy from an originator biologic to its biosimilar, have been demonstrated and endorsed in randomized and real-world studies as a viable treatment strategy. With the increasing number of available biosimilars brought to market, a new challenge arises in evaluating efficacy and safety involving all types of multiple switches that already occur in daily clinical practice (TABLE 1). To date, real-world prospective and retrospective observational studies have not reported any signs of loss of efficacy or increase in adverse events that may be entirely related to the switches. Yet, it is important to state that although many patients maintain treatment response, it has been reported therapy discontinuation after the switch[12]. It has been postulated that most of these discontinuations result from a "nocebo effect." This phenomenon, where patients with negative expectations about treatments become more likely to experience a negative outcome, has been cited by other studies[9,12,13]. A plausible justification for the nocebo effect is the mandatory switch of the reference for the biosimilar. Although the nocebo effect is observed for a few months after an NMS, it can cause demand for emergency services and increase the cost of treatment. As we have seen, it can even be the cause of discontinuation and switching back to reference[9,13]. To avoid or minimize the nocebo

TABLE 1. Multiple switches in IBD clinical practice.

Reference	Country	Number of centers	N of patients	N of switches	Biosimilars	Data collection	Follow- up
Ilias A, et al. Clin Gastroenterol Hepatol. 2019;17(12):2506-2513.e2. DOI: 10.1016/j.cgh.2018.12.036	Hungary	4	176	2	CT-P13	prospective	24 weeks
Macaluso FS, et al. Inflammatory Bowel Diseases. 2021;27(2):182-189 DOI: 10.1093/ibd/izaa036	Italy	16	276	2	CT-P13, SB2	prospective	30 weeks
Luber RP, et al Aliment Pharmacol Ther. 2021 Sep;54(5):678-688 DOI: 10.1111/apt.16497	United Kingdom	1	222		CT-P13, SB2	prospective	50 weeks
Hanzel J, et al. Inflamm Bowel Dis. 2022 Mar 30;28(4):495-501 DOI: 10.1093/ibd/izab099	Netherlands	2	193	2	CT-P13, SB2	prospective	52 weeks
Gros B, et al. United European Gastroenterol J. 2023 Mar;11(2):179-188 DOI: 10.1002/ueg2.12357	United Kingdom	1	297	3	CT-P13, SB2	prospective	250 days
Hou JC, et al. J Crohn Colitis. 2024 18(1): i1337 P708 DOI: jjad212.0838	United States	1	789	2	CT-P13	retrospective	52 weeks

effect, rather than a mandatory switch, shared decision-making between the physician and the patient should be the best strategy before the change[3,9,14,15]

So, are we ready for multiple switches between reference products and biosimilars? The answer is YES. The rationale for this response is based on robust scientific and clinical evidence accumulated over the past decade following the approval of the first biosimilar monoclonal antibody. Although skepticism was warranted, the available data support the single switch since no significant differences regarding clinical effectiveness or serious safety concerns have been demonstrated. Most patients remain on biosimilars at final follow-up, and no substantial changes in therapeutic drug monitoring were observed (TABLE 1). Regarding multiple switches, although clinical experience over the last few years may still be relatively recent, prospective observational studies have demonstrated effectiveness and safety data in a similar way to those observed with a single switch. This is so true that the EMA in late 2022 published a document declaring that all monoclonal biosimilars are interchangeable. We believe that multiple switches can be carried out effectively and safely, but this does not negate the need for appropriate counseling, objective assessment of disease activity and potential side effects prior to switching, and careful follow-up post-switch. This approach will help to ensure optimal patient care while helping to achieve the financial benefits of a switch policy[14,15].

Authors' contribution

Teixeira FV: writing and reviewing the manuscript. Peyrin-Biroulet L: reviewing the manuscript. Danese S: reviewing the manuscript.

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