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Biosimilars in Inflammatory Bowel Diseases: General Concepts and Clinical Implications

*Sabrina Rodrigues de Figueiredo,
Ana Elisa Rabe Caon, Rogerio Saad Hossne,
Fábio Vieira Teixeira, Sabine Murakami Winkler
and Natália Sousa Freitas Queiroz*

Abstract

The treatment of inflammatory bowel disease (IBD) has changed over time with the increasing use of biologics to achieve therapeutic goals. As a result, the cost of treatment increased considerably, making it necessary to develop strategies that could increase access to biological therapies. In this scenario, the biosimilars were developed with the aim of reducing costs, maintaining safety and efficacy compared to the originator. Initially, its use in IBD was based on the extrapolation of studies in other specialties, such as rheumatology. More recently, studies in inflammatory bowel disease have emerged, with favorable results for its use. It is known that there are still knowledge gaps in the use of biosimilars and more experience is needed to increase clinicians' confidence in their clinical practice. This chapter proposes a review of what is currently known about biosimilars in IBD. It discusses about aspects such as safety, efficacy, interchangeability, immunogenicity and switches.

Keywords: treatment, inflammatory bowel disease, biological therapies, biosimilar, the originator, safety, efficacy, interchangeability, immunogenicity, switch, adverse effects

1. Introduction

Biologic therapies, notably the monoclonal antibodies, changed dramatically the scenario of inflammatory bowel diseases (IBD) treatment in the past years. However, such medications have high costs that can limit patient's access to them [1–3]. In 2016, monoclonal antibodies represented only 1% of all biologic medications distributed by the Brazilian Public Health System, but 32% of expenses in biologic products [4]. Additionally, evolving treatment goals for IBD patients aiming deep remission and mucosal healing increased the use of biologics in treatment algorithms [5]. As demand becomes greater and the patents of older biologic therapies are expiring, the interest in marketing comparable versions of the reference products (RP) also increases.

Biosimilars are biologic medications resembling the RP, without clinically significant differences in safety and efficacy. Biosimilars have the potential to expand access to

biological therapies due to price competition and cost savings [1–3]. An analysis elaborated by the Johns Hopkins Bloomberg School of Public Health found that biosimilar price represented 68% of the RP price for infliximab in 2018 in the US and estimated a saving of \$407 million to up to \$1.4 billion in the same year if full biosimilar substitution of infliximab was supported by all employers who self-insure health coverage [6].

Following the expiration of Remicade® patent, CT-P13 was the first infliximab biosimilar to be approved by European Medicine Agencies (EMA) in 2013 after two clinical trials. The studies PLANETAS and PLANETRA compared CT-P13 to the RP in patients with ankylosing spondylitis and rheumatoid arthritis, respectively [7, 8]. In April 2015, the Brazilian Health Regulatory Agency (ANVISA) approved the first biosimilar of infliximab, Remsima® (Celltrion) [9] and, since then, there are three infliximab and three adalimumab biosimilars approved in Brazil (AMGEVITA™, HYRYMOZ® and Xilbrilada®). **Tables 1** and **2** summarize all approved biosimilars from infliximab and adalimumab by FDA, EMA and ANVISA.

This chapter explores general concepts of biosimilars and their implications in clinical practice in the context of inflammatory bowel diseases (IBD) treatment. We aim to summarize the positions of various scientific associations in the IBD field with respect to biosimilars and provide real-life data regarding their effectiveness and safety in countries where they have been used. In addition, the authors will focus on relevant questions encountered in the clinic, including issues related to switch, biosimilar knowledge among IBD specialists and nocebo effect.

Non-proprietary name (NPN) (US)	US	EU	Brazil	Marketing authorization holder (MAH)	Investigational medicinal product (IMP)
adalimumab-atto	Amjevita	Amgevita*	Amgevita*	Amgen	ABP501
adalimumab-adbm	Cyltezo	—	—	Boehringer Ingelheim	BI695501
adalimumab-adaz	Hyrimoz	Hyrimoz*	Hyrimoz*	Sandoz	GP2017
adalimumab-bwwd	Hadlima	Imraldi*	—	Samsung Bioepis	SB5
adalimumab-fkjp	Hulio	Hulio*	—	Mylan	FKB327
adalimumab-afzb	Abrilada	Amsparity	Xilbrilada	Pfizer/Wyeth	PF-06410293
—	—	Idacio*	Idacio	Fresenius Kabi	MSB11022

*Marketed.

Table 1.
Biosimilars for adalimumab approved by health authority. Correct of February 2021.

Non-proprietary name (NPN) (US)	US	EU	Brazil	Marketing authorization holder (MAH)	Investigational medicinal product (IMP)
infliximab-abda	Renflexis*	Flixabi*	Renflexis	Samsung	SB2
infliximab-qbtx	Ixifi	Zessly ¹ *	Xilfya*	Pfizer/Sandoz ¹	PF-06438179
infliximab-axxq	Avsola*	—	Avsola	Amgen	ABP710
infliximab-dyyb	Inflectra*	Remsima/ Inflectra*	Remsima*	Celltrion	CT-P13

¹Licensed by Sandoz in EU.

*Marketed.

Table 2.
Biosimilars for infliximab approved by health authority. Correct of February 2021.

2. Effectiveness and safety of biosimilars in IBD patients

Biosimilar uptake is increasing worldwide and accumulating evidence has been demonstrating the efficacy and safety of these drugs for the treatment of IBD patients [10–16]. **Figure 1** illustrates biosimilars for infliximab and adalimumab in the pipeline.

However, most data on biosimilars in IBD originate from real-life experience after switching from a reference biologic to a biosimilar [17] and the available randomized controlled studies comparing the reference biologic and biosimilars often had a short-term follow-up [18].

Ye et al. conducted the first randomized, multicenter, double-blind, phase 3 and non-inferiority study evaluating the efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn’s disease (CD). Patients were randomly assigned (1:1:1:1) to receive CT-P13 then CT-P13, CT-P13 then infliximab, infliximab then infliximab or infliximab then CT-P13, with switching occurring at week 30. The primary endpoint was the proportion of patients with a decrease of 70 points or more in the Crohn’s Disease Activity Index (CDAI) at week 6. Response rates were similar between the two groups (CT-P13: 69.4%, CI 95%: 59.9–77.8 vs. IFX: 74.3%, CI 95%: 65.1–82.2), establishing the non-inferiority of CT-P13 in relation to IFX [18]. Accordingly, in a prospective, observational and multicentre study, Gece et al. evaluated the efficacy, safety and immunogenicity of CT-P13 in the treatment of CD induction ($n = 126$) and ulcerative colitis (UC- $n = 84$). Remission, clinical and biochemical response were assessed at week 14, corticosteroid-free clinical remission at week 30 and therapeutic drug level was monitored. After 14 weeks of treatment, 81.4% of patients with CD and 77.6% of patients with UC presented clinical response and 53.6% of patients with CD and 58.6% of those with UC achieved clinical remission, according to the CDAI and partial Mayo score. The rates of clinical remission were higher in patients not previously exposed to IFX. Infusion reactions and serious adverse events occurred in 6.6% of patients with CD and 5.7% of patients with UC. The authors concluded that CT-P13 is safe and effective in inducing remission and clinical response in both CD and UC [19].

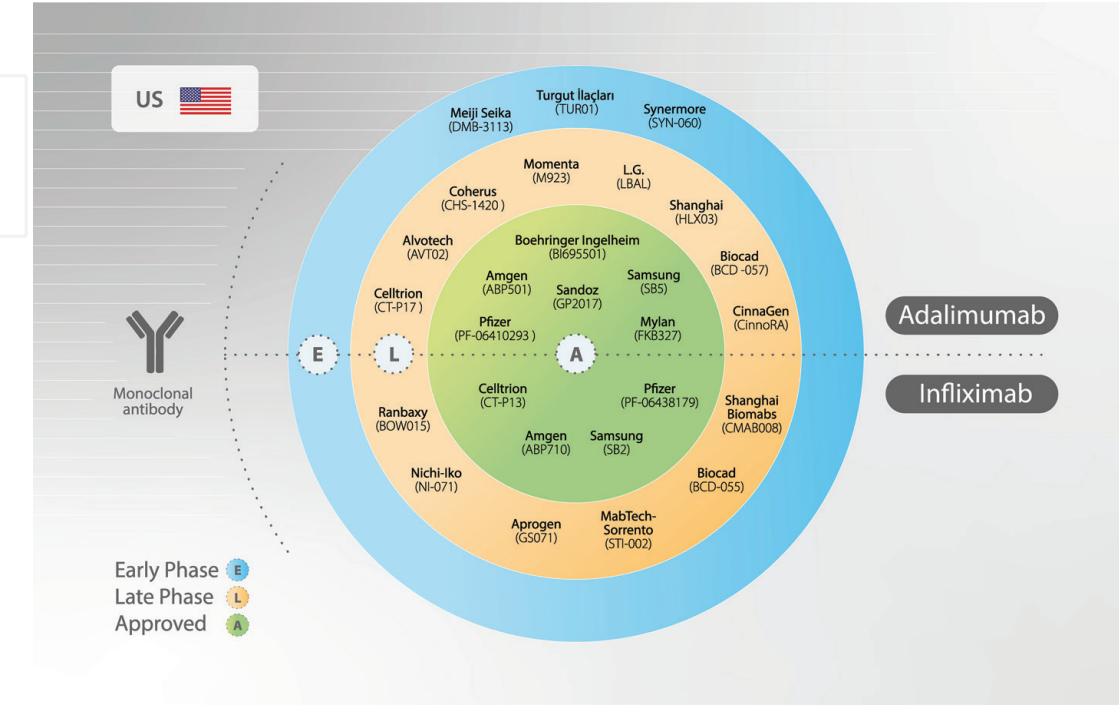


Figure 1.
Biosimilars for infliximab and adalimumab.

A recent systematic review and meta-analysis by Queiroz et al. assessed the risk and reasons for drug discontinuation in the IBD population that switched from the originator to biosimilars in real-world studies [20]. A total of 30 observational studies comprising 3594 IBD patients who switched from originator biologics to biosimilar with a mean follow-up period over 6 months and a mean duration of treatment with the originator reported as over 1 year were included. In addition, the reasons for treatment discontinuation were extracted and meta-analyzed. The discontinuation rates after a switch were 8, 14 and 21% after 6, 12, and 24 months, respectively. The main reasons for discontinuation were as follows: increased loss of response (2%), remission (4%), loss of adherence (4%), adverse effects (5%) and loss of response (7%). Quality of evidence varied from low to very low depending on the analyzed outcome. The nocebo effect was explicitly analyzed as a reason for discontinuation in only one study [21], and the frequency of reported subjective adverse events was low. It is important to emphasize that most of the studies included in this review did not disclose important information that could have influenced the results, such as disease activity at the moment of switch and drug trough levels before and after switch. This study raises awareness for the urgent need to conducting prospective studies evaluating long-term outcomes associated with the switch of biological therapy in IBD patients.

3. Position statements from different IBD societies (CCFA, ECCO, GEDIIB)

In 2015, a task force of three Brazilian medical societies involved in the treatment of immune-mediated diseases (gastroenterology, rheumatology and dermatology) has first issued guidance on the utilization of biosimilars [22]. Since the approval of CT-P13 in Brazil, several IBD societies worldwide have issued position statements regarding the use of biosimilars for the treatment of Crohn's disease and ulcerative colitis [22–26]. What is still a huge discussion in the medical literature, indeed, is the switch or transition between biologics: innovator to biosimilar, biosimilar to innovator and biosimilar to other biosimilar. The main recommendations from different IBD societies are summarized as follows:

- a. GEDIIB (Grupo Brasileiro da Doença Inflamatória Intestinal do Brasil): The Brazilian IBD Study Group advises all members about the entry of biosimilars into the Brazilian pharmaceutical market. The guidelines highlighted some important points regarding the switch between biological drugs, which must be carried out with the consent of both the attending physician and the patient [24]. GEDIIB also acknowledge the effectiveness and safety of the biosimilar used in naïve patients as well as in situations of a single switch (original to biosimilar or vice versa).

In fact, what is not clear so far is the ideal time for this switch. Considering switch from biologics innovator to biosimilar, GEDIIB acknowledges the following:

1. We should not switch if clinical response was not achieved with the initial biological therapy.
2. Before switching, patient must be stable on clinical remission based on clinical, laboratorial and endoscopic data.
3. There should be no suspicion or report of any immunogenicity reaction with the initial biological therapy before switching.

b. ECCO (European Crohn's and Colitis Organization): In 2017, ECCO have published a positioning statement regarding biosimilars. All other European IBD societies follow the same ideas of ECCO [25]:

1. Once a biosimilar is registered in the European Unit by the EMA (European Medical Agency), this product should be considered efficacious and safe to be used.
2. ECCO acknowledges that biosimilarity is better characterized by performing suitable *in vitro* assays than clinical studies. Moreover, clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. On the other hand, demonstration of safety of biosimilars requires large observational studies, which may be achieved by registries provided by all players somehow involved in the treatment of IBD patients: healthcare professionals, patients' associations and pharma industry.
3. ECCO also acknowledges transitioning from the originator to a biosimilar in IBD patients. Observational switching studies can provide valuable evidence concerning safety and efficacy. Scientific and clinical evidence is still lacking regarding reverse switching, multiple switching and cross-switching among biosimilars in IBD patients.
4. It is consensus between the main societies that switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

c. CCFA (Crohn's and Colitis Foundation of America) is a professional organization for those physicians, nurses, scientists and other health providers who care for IBD patients in United States. CCFA support all decision of the Food and Drug Administration (FDA) regarding biosimilar approval and its role in ensuring safety of patients. CCFA also acknowledges that all biologicals, innovator or biosimilar should undergo through human testing and meet the highest safety standards. Considering interchangeability, CCFA urges the FDA to provide reasonable proof that switching from originator to the biosimilar would not incur in immunogenicity or loss of response to the innovator, and vice versa.

In summary, IBD societies (ECCO, GEDIIB and CCFA) support a single transition between biologicals, as long as the patients are on clinical remission. Moreover, CCFA believes that when any transition occurs, both patient and physician must be informed of the exact drug the patient is receiving. In agreement with other societies, CCFA does not support multiple switches due to lack of clinical and scientific evidence [26].

4. Different scenarios: double switch, cross switch, switch back

4.1 Overview of interchangeability

Nowadays, what is really being discussed at the medical literature is interchangeability between biological products. The American FDA defined that

interchangeability is when the product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between a candidate interchangeable biologic and its reference product should be evaluated by a clinical study specifically designed for these endpoints [27, 28]. Once approved by FDA's high standards, an interchangeable biologic may be substituted by biosimilar or vice versa, without any involvement of the prescriber [27, 28].

On the other hand, EMA has reported a totally different definition regarding interchangeability of biologics. For the European group, FDA's perception of interchangeability is based in the American legislation and corresponds to an automatic substitution by the European agency terminology. Biosimilars are copy versions of an already existing biological product and approved by a regulatory agency. Then, it is expected to be a high-quality product, efficacious and safe. Because of the high similarity to the innovator, EMA believes that there is no reason for the immune system of the treating patients to respond differently than when the same patient was exposed to the innovator product. That is why EMA advocates that interchangeability is not a legal but a scientific and medical term. Once approved as a biosimilar, it can be interchangeable. EMA regulators stated that they have no intention to create a new legal regulatory requirement for interchangeability of biologics. Indeed, European regulators believe that this dichotomy would create two classes of biosimilars: the interchangeable (approved after being evaluated in a clinical trial specifically designed as required by FDA) and those not interchangeable [28, 29].

In Brazil, so far, health authorities did not issue any specific regulation regarding interchangeability of biological products. A technical note published by ANVISA in October 2018 concluded that interchangeability and substitution are more directly related to clinical practice than to regulatory status. Moreover, ANVISA believes that interchangeability and substitution involve broader aspects, such as specific studies conducted by companies, data from the literature, medical evaluation in each case and cost-effectiveness. Moreover, the Brazilian agency also reported the importance of a medical evaluation and adequate pharmaceutical care in the case of switching from an innovator to a biosimilar. ANVISA also believes that multiple exchanges between biosimilar products and the comparator biological product are not suitable, and traceability and monitoring of use are very difficult in these cases. In fact, ANVISA gave to both, the prescriber physician and the Brazilian Ministry of Health, power to decide about switching between biological products [30]. However, without any recommendation and regulation, unusual scenarios of multiple switches may occur and the appropriate pharmacovigilance will be impaired, compromising the safety of the treatment.

4.2 Single switch

Since the approval of the first monoclonal antibody biosimilar, CT-P13, by the EMA, several observational studies reported the effectiveness and safety of a single switch between a biologic reference and a biosimilar in the IBD's treatment scenario [31]. Others have reported a significant cost savings with the treatment after incorporating biosimilar in the medical practice. On the basis of these findings, it would be likely that switching to biosimilars would no longer be an option but the routine approach for patients who are candidates for biological drugs [32, 33]. However, it has been observed at the literature some problems regarding switching from originator to biosimilars. Chaparro and colleagues in Spain reported a series with almost 200 IBD patients who switch from infliximab reference to CT-P13 and

compared the results to patients kept on the originator. Authors observed higher rates of relapse on the switching group. The cumulative incidence of relapse was 2% at 6 months and 10% at 24 months. In the multivariate analysis, the switch to CT-P13 was associated with a higher risk of relapse (HR = 3.5, 95% confidence interval [CI] = 2–6) [34]. A recent systematic review and metaanalysis by Queiroz et al. reported that discontinuation rates following a switch to a biosimilar in patients with IBD increase over time [20]. Moreover, not long ago, a study by IQVIA analyzed a very large database of German patients with immuno-mediated diseases treated with biologics, which includes ~60% of all prescriptions reimbursed by statutory health insurance funds in Germany [35]. Approximately 30% of patients switched back from an etanercept/infliximab biosimilar to an etanercept/infliximab reference product within 12 months after the initial biosimilar therapy. The authors found no significant effect of different factors, such as age, gender, physician specialty and concomitant therapy [35]. It was speculated by the academic community that discontinuation of the treatment may occur due to a nocebo effect.

Recent studies have assessed the safety and effectiveness of switching to other infliximab biosimilars that became available after CT-P13 and to adalimumab biosimilar. A prospective and observational Germany cohort study described the 80-week follow-up of 144 patients with inflammatory bowel disease after switching from infliximab to a biosimilar (SB2). The same recommendations for the use of infliximab were maintained for the new drug. All patients received infliximab induction and the time to switch to the biosimilar was variable (the mean duration of previous infliximab therapy was 30 months). Most patients were in remission at the time of switch, 36% had mild to moderate clinical activity and none had severe activity. Despite the limitations of the study, it was observed that the disease activity was not affected by the transition to biosimilar, the switching was not associated with lack of effectiveness and was well tolerated [36].

An observational cohort study included 481 patients treated with SB5 (Sb5-switch cohort and SB5-start cohort) over 12 months of follow-up. The biosimilar was effective and safe. The observed rates of primary non-response and secondary loss of response in the switched cohort were similar to those previously reported to the originator [37].

4.3 Reverse, cross-switch and multiple switches

Reverse, multiple and cross-switches will be a challenge for the next years to come. It has been incorporated in clinical practice the need to switch from an originator to a biosimilar. Moreover, some new demanding situations already have come to the biosimilar era. We clinicians now face not only a single switch but also the switch in the opposite direction, for instance, when relapse or adverse effect are observed after a switch between biologics. Furthermore, we will face, in the next months or years, multiple switches among different molecules from one biosimilar to another—named cross-switch. However, we do not have strong evidence to support this new kind of switches. Few observational studies have been reported so far. Ilias and co-authors analyzed 174 patients with Crohn and ulcerative colitis in maintenance therapy with CT-P13 who switched back to reference infliximab due to reimbursement policies in Hungary. No significant changes were observed in remission, trough levels or antidrug antibodies in patients switched from the biosimilar to remicade. No new safety signals were detected [38].

For the very first time, an Italian group has reported multiple switches in IBD. The Sicilian Network for Inflammatory Bowel Disease group analyzed almost 230 patients: 127 (46.0%) were naïve to IFX and naïve to anti-TNFs, 65 (23.5%) were naïve to infliximab and previously exposed to anti-TNFs, 17 (6.2%) were switched

from an infliximab reference to a biosimilar (SB2), 43 (15.6%) were switched from the biosimilar CT-P13 to SB2 and 24 (8.7%) were multiply switched (from infliximab reference to CT-P13 and to SB2) [39]. They observed 67 serious adverse in 57 patients (20.7%; incidence rate: 36.7 per 100 patient-year) and 31 of these events lead to withdrawal. The effectiveness after 8 weeks of treatment was evaluated in patients naïve to IFX ($n = 192$): 110 patients (57.3%) had steroid-free remission, while 56 patients had no response (29.2%). At the end of follow-up, 26.1% interrupted the treatment, without any significant differences in treatment persistency, (log-rank $P = 0.15$). Finally, results of 52 IBD patients who double switch was compared with those of 66 IBD patients switched from originator to CT-P13 (infliximab reference to CT-P13 and then to SB2). Almost 50% of them were in clinical remission in the double switch group after a median follow-up of 40 weeks and only six adverse effects occurred, which lead to discontinuation in three cases (6%) [40].

A prospective multicenter cohort study evaluated the effectiveness and safety of multiple switches in inflammatory bowel disease. One hundred and seventy-six patients were included and divided into three groups (Originator to CT-P13, CT-P13 to SB2 and Originator to CT-P13). Patients had variable previous duration of IFX exposure before index switch (minimum median of 1.9 years), mostly in clinical remission. The dose and interval were maintained after the switch and were only modified if clinically necessary. Similar rates of clinical and biochemical remission were observed in the three groups at 12 months after the most recent switch. Increased immunogenicity was not observed after multiple successive switches [41].

A Dutch multicenter retrospective study assessed the need for reverse switch to infliximab among patients with inflammatory bowel disease using biosimilars (CT-P13). Among 758 patients who switched to CT-P13 after median of 4.7 years of treatment with originator, reverse switching was observed in almost 10% of patients mainly due to gastrointestinal and dermatological symptoms. In nine patients, the reason for switching was loss of response. No relevant differences in pharmacokinetics or immunogenicity were observed. Reverse switching was beneficial in 73.3% of patients and may be considered in case of loss of response or adverse effects following an initial switch [42].

As the reader may see, we just have few reports regarding multiple switches and cross-switch reported in the literature. Further experience in different scenarios will certainly fill in the knowledge gaps and pave the way to increase clinicians' confidence in their clinical practice.

5. Nocebo effect in IBD

Almost one decade after the first approval of a monoclonal antibody biosimilar by the EMA in 2013 [43], an underestimated phenomenon has been observed in patients treated with biological drugs: the nocebo effect [44–47].

Biological treatment is currently part of the medical practice in inflammatory bowel disease management. However, as already discussed in this chapter, the higher cost of the treatment of immune-mediated diseases is directly related to the cost of biological drugs. In this scenario, biosimilar drugs were created. No long ago, higher-than expected discontinuation of treatment rates possible related to nocebo effect has been observed in patients who switched from a stable treatment with the originator infliximab to the biosimilar CT-P13 [20].

Nocebo effect is a physiological, psychological and neurobiological phenomenon related to a perceived harm that occurs as a consequence of patients' negative expectations not associated with known pharmacologic actions of the treatment. More recently,

after the beginning of the biosimilar era, the concept of nocebo was revisited and defined as the negative equivalent of the placebo effect. Since then, this concept has received considerable attention in both clinical research and clinical practice [44–46]. Even though medical evidence supports biosimilar use, several barriers were created to hinder more widespread adoption of these drugs into current medical practice. Slow uptake of biosimilars in clinical practice may reflect gaps in patients' and clinicians' knowledge and understanding of these drugs risks and benefits. For sure, this fact has stimulated interest in the potential role of nocebo phenomenon [20, 47, 48].

It has been proposed that different neurobiological pathways may play a role in the effect of negative expectations on patients' perceptions. In fact, the majority of the studies came from the field of pain perception, a method to better understand nocebo effect. Some pathways were supposed to be involved: activation of the hypothalamic-pituitary-adrenal axis and CCKergic systems (CCK = cholecystokinin), as well as decreasing dopamine and opioid activity may play a role in the pathophysiology of nocebo effect. The neuroanatomical regions contributing to the nocebo effect are most likely different than those contributing to the placebo effect [48].

Odinet and colleagues analyzed the nocebo effect in a systematic review. Authors concluded that there are insufficient data published to confirm a biosimilar nocebo effect, although higher discontinuation rates in infliximab biosimilar open-label studies support this theory. They also outlined many limitations in this systematic review to draw strong conclusions. Further studies are needed to evaluate the existence of a biosimilar nocebo effect. If it does indeed exist, the effects of mitigation strategies such as prescriber education and patient empowerment should be evaluated [47].

The nocebo effect, at least in part, may be responsible for higher rates of discontinuation of treatment after switching from an innovator biological to a biosimilar. In the aforementioned systematic review and metaanalysis by Queiroz et al., our group reported that discontinuation rates following a switch to a biosimilar in patients with IBD increase over time. However, it was not possible to confirm the nocebo effect as the unique reason for discontinuation [20].

6. Biosimilar knowledge among IBD specialists

In the earliest years of marketing of biosimilars, the perspective of IBD specialists regarding biosimilars was very conservative [49]. Previous survey-based studies with gastroenterologists have shown a significant unawareness of biosimilar medications in general [50, 51]. On the other hand, it has been previously demonstrated that educational initiatives can increase confidence regarding biosimilar use in clinical practice [52]. Little is known about the comprehension and perception of Brazilian gastroenterologists about biosimilars. In 2016, the Brazilian Study Group of Inflammatory Bowel Diseases (GEDIIB) conducted an anonymous web-based survey with IBD-expert gastroenterologists regarding their current knowledge of biosimilar monoclonal antibodies. The volunteers responded to 22 multiple-choice questions contemplating issues such as their confidence and concerns of using biosimilars, their opinion about non-medical switching and their need of educational activities. To evaluate changes in perception of specialists, a similar follow-up questionnaire with 14 multiple-choice questions was later developed by the GEDIIB. It was delivered during the II Brazilian Congress of Inflammatory Bowel Diseases audience, between March 29 and 31, 2019. Both surveys were non-interventional and offered self-selective recruitment. A simple descriptive comparison of data between the two questionnaires was carried out.

6.1 2016 survey demographics

A total of 61 respondents replied to the survey. Most worked in private clinics (72%) and in public hospitals (49%), and 70% occupied high positions, such as professors, head of Gastroenterology departments and head of IBD units. The majority of them lived in the southeastern region, where the most developed IBD referral centers are located in Brazil. In total, 95% answered that they were responsible for biologic therapy prescription and two-thirds of them had more than 5 years of experience in prescribing biologics.

6.2 2019 survey demographics

The similar questionnaire was applied to 731 gastroenterology physicians. Most of the volunteers responded that they lived in the southeastern region, 41% worked in public hospitals, while 39% worked in private clinics. The majority of the physicians (67%) declared to have access to biosimilars; however, 40% had never prescribed the medication.

6.3 Comparing the survey results

The majority of participants considered that biosimilars are less expensive (77% in 2016; 86% in 2019) than the originator. In both surveys, about half of the responders thought that biosimilars have equivalent efficacy, and about 14% thought that biosimilars will have more indications than the originator. In 2019, a much lower percentage of participants considered that the immunogenicity of biosimilars is the same than the originator (21% compared to 47% in 2016). **Figure 2** summarizes the answers to general concepts of biosimilars.

The majority of responders disagreed with substitution of the originator with a biosimilar by a pharmacist (82% in 2016; 92% in 2019), although, in 2019, 8% agreed with automatic substitution only for new prescriptions. When asked if they would switch a patient in remission from the originator to a biosimilar, most (92% in 2019) responded they would not make a switch, even in patients with sustained remission. **Figure 3** illustrates the responses regarding substitution and switch.

Expert gastroenterologists still show concerns regarding the efficacy and safety when prescribing biosimilars. The percentage of totally confident and very confident to prescribe these medications decreased from 23% in 2016 to only 4% in 2019, while 56% of respondents were little confident and 21% have no confidence in prescribing this medication in 2019—worse compared to 2016. **Figure 4** summarizes confidence in biosimilars.

In the 2019 survey, 59% of participants reported that education in biosimilars is confusing and the majority agreed that educational activities involving biosimilars are needed (94%), as well as greater collaboration between societies to develop guidelines in biosimilars (95%) and the development of records for monitoring the safety of biosimilars (99%).

In a recent similar survey, European IBD physicians were asked about the use of biosimilars in 2013 and 2015. Unlike our research, their study demonstrated that a better understanding of the process of developing biosimilars and their regulatory process contributed to a change in the perception of IBD experts about biosimilars and, consequently, they became more confident in prescribing biosimilars [52]. Conversely, in our study, there was a worsening in the confidence of IBD physicians in prescribing biosimilars over time. This difference between the European and Brazilian surveys may reflect the lack of knowledge of Brazilian physicians about biosimilars and shed light for the development of appropriate educational strategies in Brazil.

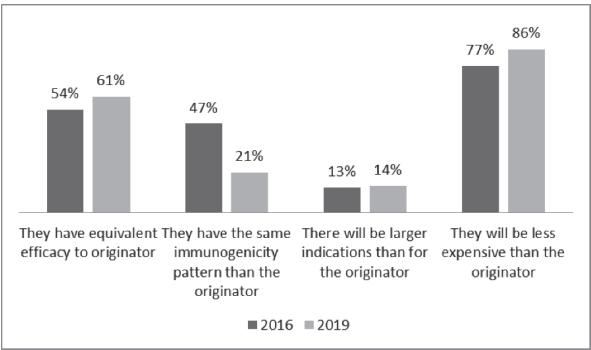


Figure 2.
General concepts of biosimilars in 2016 and 2019.

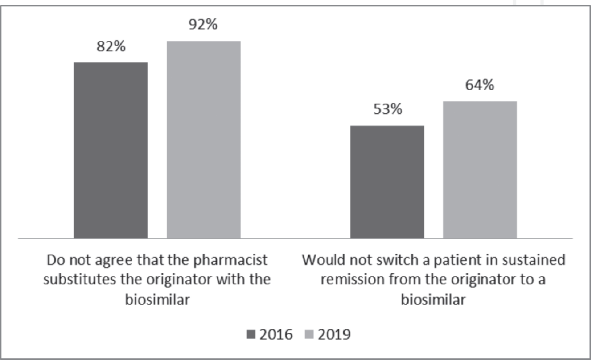


Figure 3.
Responses regarding substitution and switch in 2016 and 2019.

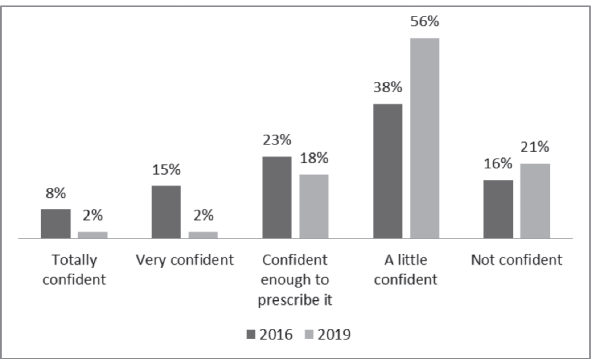


Figure 4.
Confidence in biosimilars in 2016 and 2019.

7. Conclusions

As the patents of biologics are expiring, biosimilars represent a promising opportunity to expand access to biological therapies due to price competition and cost savings. Although this chapter provides a comprehensive overview of the current state of knowledge on biosimilars in IBD, knowledge gaps remain, especially concerning different strategies of switching (e.g., cross-, multiple-). The widespread adoption of biosimilars will enable increasing knowledge and experience with biosimilars, which will pave the way toward an improved acceptance and decreased negative expectations with the incorporation of these drugs in clinical practice.

Author details

Sabrina Rodrigues de Figueiredo¹, Ana Elisa Rabe Caon¹, Rogerio Saad Hossne², Fábio Vieira Teixeira³, Sabine Murakami Winkler⁴ and Natália Sousa Freitas Queiroz^{1*}

1 Faculdade de Medicina, Departamento de Gastroenterologia, Universidade de São Paulo, São Paulo, Brazil

2 Cirurgia Digestiva, Universidade Estadual Paulista (UNESP), Botucatu, Brazil

3 Gastrosáude – IBD Clinic, Marília, Brazil

4 Independent Researcher, São Paulo, Brazil

*Address all correspondence to: nataliafreitas10@yahoo.com.br

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References

- [1] Kim H, Alten R, Avedano L, Dignass A, Gomollón F, Greveson K, et al. The future of biosimilars: Maximizing benefits across immune-mediated inflammatory diseases. *Drugs*. 2020;**80**(2):99-113
- [2] Gulacsi L, Pentek M, Rencz F, Brodszky V, Baji P, Vegh Z, et al. Biosimilars for the management of inflammatory bowel diseases: Economic considerations. *Current Medicinal Chemistry*. 2019;**26**(2):259-269
- [3] Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: From theory to practice. *Nature Reviews. Gastroenterology & Hepatology*. 2017;**14**(1):22-31
- [4] Muller GG. Technical and regulatory evaluation of quality requirements for the registration of human biological and biosimilar drugs: Perspectives and challenges in Brazil [master thesis]. São Paulo: Faculty of Pharmaceutical Sciences, University of São Paulo; 2018
- [5] Ungaro R, Colombel JF, Lisssoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis. *The American Journal of Gastroenterology*. 2019;**114**(6):874-883
- [6] Socal M, Ballreich J, Chyr L, Anderson G. Biosimilar Medications—Savings Opportunities for Large Employers. A Report for ERIC—The ERISA Industry Committee. Baltimore: Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; 2020
- [7] 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. *Annals of the Rheumatic Diseases*. 2013;**72**:1605-1612
- [8] 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. *Annals of the Rheumatic Diseases*. 2013;**72**(10):1613-1620
- [9] ASCOM. Primeiro medicamento biológico por comparabilidade é registrado pela Anvisa [Homepage on the Internet]. Available from: http://antigo.anvisa.gov.br/noticias/-/asset_publisher/FXrpx9qY7FbU/content/primeiro-medicamento-biologico-por-comparabilidade-e-registrado-pela-anvisa/219201/pop_up?_101_INSTANCE_FXrpx9qY7FbU_viewMode=print&_101_INSTANCE_FXrpx9qY7FbU_languageId=pt_BR [Accessed: 27 April 2015]
- [10] Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): A 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;**389**:2304-2316
- [11] Meyer A, Rudant J, Drouin J, Weill A, Carbonnel F, Coste J. Effectiveness and safety of reference infliximab and biosimilar in Crohn disease: A French equivalence study. *Annals of Internal Medicine*. 2019;**170**:99-107
- [12] Strik AS, van de Vrie W, Bloemsaat-Minekus JPJ, Nurmohamed M, Bossuyt PJJ,

- Bodelier A, et al. Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): An open-label, multicentre, phase 4 non-inferiority trial. *The Lancet Gastroenterology & Hepatology*. 2018;**3**:404-412
- [13] Fiorino G, Manetti N, Armuzzi A, Orlando A, Variola A, Bonovas S, et al. The PROSIT-BIO cohort: A prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilar. *Inflammatory Bowel Diseases*. 2017;**23**(2):233-243
- [14] Petitdidier N, Beaugerie L, Carbonnel F, Bourrier A, Treton X, Rajca S, et al. Real-world use of therapeutic drug monitoring of CT-P13 in patients with inflammatory bowel disease: A 12-month prospective observational cohort study. *Clinics and Research in Hepatology and Gastroenterology*. 2020;**44**(4):609-618
- [15] Bernard EJ, Fedorak RN, Jairath V. Systematic review: Non-medical switching of infliximab to CT-P13 in inflammatory bowel disease. *Digestive Diseases and Sciences*. 2020;**65**(8): 2354-2372
- [16] Ben-Horin S, Yavzori M, Benhar I, Fudim E, Picard O, Ungar B, et al. Cross-immunogenicity: Antibodies to infliximab in remicade-treated patients with IBD similarly recognize the biosimilar remsima. *Gut*. 2016;**65**:1132-1138
- [17] Avouac J, Moltó A, Abitbol V, Etcheto A, Salcion A, Gutermann L, et al. Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: The experience of Cochin University Hospital, Paris, France. *Seminars in Arthritis and Rheumatism*. 2019;**47**(5):741-748. DOI: 10.1016/j.semarthrit.2017.10.002
- [18] Ye BD, Pesegova M, Alexeeva O, Osipenko M, Lahat A, Dorofeyev A, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: An international, randomised, double-blind, phase 3 non-inferiority study. *Lancet*. 2019;**6736**(18):1-9
- [19] Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: A prospective, multicentre, nationwide cohort. *Journal of Crohn's & Colitis*. 2016;**10**(2):133-140
- [20] Queiroz NSF, Saad-Hossne R, Fróes RDSB, Penna FGCE, Gabriel SB, Martins AL, et al. Discontinuation rates following a switch from a reference to a biosimilar biologic in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Arquivos de Gastroenterologia*. Jul-Sep 2020;**57**(3):232-243. DOI:10.1590/s0004-2803.202000000-45
- [21] Boone NW, Liu L, Romberg-Camps MJ, Duijsens L, Houwen C, van der Kuy PHM, et al. The nocebo effect challenges the non-medical infliximab switch in practice. *European Journal of Clinical Pharmacology*. 2019;**74**(5): 655-661
- [22] Azevedo VF, Meirelles ES, Kochen JA, Medeiros AC, Miszputen SJ, Teixeira FV, et al. Recommendations on the use of biosimilars by the Brazilian Society of Rheumatology, Brazilian Society of Dermatology, Brazilian Federation of Gastroenterology and Brazilian Study Group on Inflammatory Bowel Disease—Focus on clinical evaluation of monoclonal antibodies and fusion proteins used in the treatment of autoimmune diseases. *Autoimmunity Reviews*. 2015;**14**(9):769-773
- [23] Teixeira FV, Kotze PG, Damião AO. ANVISA approves the first biosimilar monoclonal antibody based on

comparability in Brazil. *Arquivos de Gastroenterologia*. 2016;**53**(2):60-61

[24] Comissão de Medicamentos e Biossimilares do Grupo de Estudos da Doença Inflamatória Intestinal do Brasil (GEDIIB). Posicionamento oficial sobre a entrada de novos medicamentos biossimilares no mercado farmacêutico brasileiro. São Paulo: GEDIIB; 2020. Available from: <https://gediib.org.br/noticias/posicionamento-oficial-sobre-a-entrada-de-novos-medicamentos-biossimilares-no-mercado-farmacutico-brasileiro> [Accessed: 27 February 2021]

[25] Danese S, Fiorino G, Raine T, Ferrante M, Kemp K, Kierkus J, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease—An update. *Journal of Crohn's & Colitis*. 2017;**11**(1):26-34

[26] Crohn's and Colitis Foundation. Biosimilars: Position Statement. Available from: <https://www.crohnscolitisfoundation.org/sites/default/files/2019-06/biosimilars-statement-needs.pdf> [Accessed: 27 February 2021]

[27] Title VII: Improving Access To Innovative Medical Therapies. Biologic price competition and innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA). Available from: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf> [Accessed: 27 February 2021]

[28] US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: Guidance for industry. Available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf> [Accessed: 4 March 2021]

[29] Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of biosimilars: A European perspective. *BioDrugs*. 2017; **31**(2):83-91

[30] ANVISA. Revisada nota sobre troca de produtos biológicos. Available from: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2018/revisada-nota-sobre-troca-de-produtos-biologicos> [Accessed: 4 March 2021]

[31] Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakuraba A. Systematic review with meta-analysis: The efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor- α agent (infliximab), in inflammatory bowel diseases. *Alimentary Pharmacology & Therapeutics*. 2017;**45**(8):1043-1057

[32] Razanskaite V, Bettey M, Downey L, Wright J, Callaghan J, Rush M, et al. Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme. *Journal of Crohn's & Colitis*. 2017;**11**(6):690-696

[33] Feagan BG, Gordon L, Ma C, Lichtenstein GR. Systematic review: Efficacy and safety of switching patients between reference and biosimilar infliximab. *Alimentary Pharmacology & Therapeutics*. 2019;**49**:31-40

[34] Chaparro M, Garre A, Guerra Veloz MF, Vázquez Morón JM, De Castro ML, Leo E, et al. Effectiveness and safety of the switch from Remicade® to CT-P13 in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis*. 2019;**13**:1380-1386

[35] Reuber K, Kostev K. Prevalence of switching from two anti-TNF biosimilars back to biologic reference products in Germany. *International Journal of Clinical Pharmacology and Therapeutics*. 2019;**57**(6):323-328

[36] Fischer S, Cohnen S, Klenske E, Schmitt H, Vitali F, Hirschmann S, et al.

Long-term effectiveness, safety and immunogenicity of the biosimilar SB2 in inflammatory bowel disease patients after switching from originator infliximab. *Therapeutic Advances in Gastroenterology*. 2021;14:1-16

[37] Derikx LAAP, Dolby HW, Plevris N, Lucaciu L, Rees CS, Lyons M, et al. Effectiveness and safety of adalimumab biosimilar SB5 in inflammatory bowel disease: Outcomes in originator to SB5 switch, double biosimilar switch and bio-naïve SB5 observational cohorts. *Journal of Crohn's & Colitis*. 2021 Jun 5;jjab100. DOI: 10.1093/ecco-jcc/jjab100. [Online ahead of print]

[38] Ilias A, Szanto K, Gonczi L, Kurti Z, Golovics PA, Farkas K, et al. Outcomes of patients with inflammatory bowel diseases switched from maintenance therapy with a biosimilar to remicade. *Clinical Gastroenterology and Hepatology*. 2019;17(12):2506-2513.e2

[39] Macaluso FS, Fries W, Viola A, Centritto A, Cappello M, Giuffrida E, et al. The SPOSIB SB2 sicilian cohort: Safety and effectiveness of infliximab biosimilar SB2 in inflammatory bowel diseases, including multiple switches. *Inflammatory Bowel Diseases*. 2021;27(2):182-189

[40] Mazza S, Fasci A, Casini V, Ricci C, Munari F, Pirola L, et al. Safety and clinical efficacy of double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases (SCESICS): A multicentre study presented at DDW2020. Available from: <https://ddw.apprisor.org/epsabstract/ddw.cfm?id=1> [Accessed: 8 March 2021]

[41] Hanzel JH, Jansen JM, Steege RWF, Gecse KB, D'Haens GR. Multiple switches from the originator infliximab to biosimilars is effective and safe in inflammatory bowel disease: A prospective multicenter cohort study.

Inflammatory Bowel Diseases. 2021;XX:1-7

[42] Mahmmoud S, Schultheiss JPD, van Bodegraven AA, Dijkstra G, Gilissen LPL, et al. Outcome of reverse switching from CT-P13 to originator infliximab in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2021 Nov 15;27(12):1954-1962

[43] European Medicines Agency (EMA). Remsina. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/remesima> [Accessed: 10 February 2021]

[44] Rezk MF, Pieper B. Treatment outcomes with biosimilars: Be aware of the nocebo effect. *Rheumatology and Therapy*. 2017;4(2):209-218

[45] Petit J, Antignac M, Poilverd RM, Baratto R, Darthout S, Desouches S, et al. Multidisciplinary team intervention to reduce the nocebo effect when switching from the originator infliximab to a biosimilar. *RMD Open*. 2021;7(1):e001396

[46] Pouillon L, Socha M, Demore B, Thilly N, Abitbol V, Danese S, et al. The nocebo effect: A clinical challenge in the era of biosimilars. *Expert Review of Clinical Immunology*. 2018;14(9):739-749

[47] Odinet JS, Day CE, Cruz JL, Heindel GA. The biosimilar nocebo effect? A systematic review of double-blinded versus open-label studies. *Journal of Managed Care & Specialty Pharmacy*. 2018;24(10):952-959

[48] Freeman S, Yu R, Egorova N, Chen X, Kirsch I, Claggett B, et al. Distinct neural representations of placebo and nocebo effects. *NeuroImage*. 2015;112:197-207

[49] Sullivan E, Piercy J, Waller J, Black CM, Kachroo S. Assessing gastroenterologist and patient

acceptance of biosimilars in ulcerative colitis and Crohn's disease across Germany. PLoS One. 2017; **12**(4):e0175826

[50] Cohen H, Beydoun D, Chien D, Lessor T, McCabe D, Muenzberg M, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Advances in Therapy*. 2017;**33**(12):2160-2172

[51] Danese S, Fiorino G, Michetti P. Viewpoint: Knowledge and view-points on biosimilar monoclonal antibodies among members of the European Crohn and Colitis Organization. *Journal of Crohn's & Colitis*. 2014;**8**:1548-1550

[52] Danese S, Fiorino G, Michetti P. Changes in biosimilar knowledge among European Crohn's Colitis Organization [ECCO] members: An updated survey. *Journal of Crohn's & Colitis*. 2016;**10**(11):1362-1365