ORIGINAL ARTICLE

AG-2019-177
doi.org/10.1590/S0004-2803.202000000-45

Discontinuation rates following a switch from a reference to a biosimilar biologic in patients with inflammatory bowel disease: a systematic review and meta-analysis

Natália Sousa Freitas **QUEIROZ**[1], Rogerio **SAAD-HOSSNE**[2], Renata de Sá Brito **FRÓES**[3], Francisco Guilherme Cancela e **PENNA**[4], Stefania Burjack **GABRIEL**[5], Adalberta Lima **MARTINS**[6] and Fabio Vieira **TEIXEIRA**[7]

Received: 20 December 2019
Accepted: 26 June 2020

ABSTRACT – **Background** – Biologics have revolutionized the treatment of inflammatory bowel disease (IBD). However, these drugs had a significant influence on treatment-related costs, which resulted in the development of biosimilars. **Objective** – This systematic review and meta-analysis aimed to evaluate the drug discontinuation rate in the IBD population who switched from originator to biosimilars in real-world switching studies and address potential nocebo effects as reasons for drug discontinuation. **Methods** – Medline (via PubMed), EMBASE, Cochrane Library, and abstract databases of selected congresses were screened for reports of monoclonal antibody (mAb) switching with a minimum post-switch follow-up of >6 months or three infusions. All available information on discontinuation rates was assessed. **Results** – A total of 30 observational studies were included, involving 3,594 patients with IBD. Twenty-six studies reported a switch from infliximab to CT-P13, two studies involved a switch to SB2, and switching information was not available in two studies. The discontinuation rates were 8%, 14%, and 21% at 6, 12, and 24 months, respectively. The main reasons for drug discontinuation and their respective risks were: disease worsening (2%), remission (4%), loss of adherence (4%), adverse events (5%), and loss of response (7%). The quality of the evidence ranged from low to very low depending on the outcome analyzed. Subjective symptoms leading to drug discontinuation were infrequently reported, and the nocebo effect was clearly assessed in just one of the included papers. **Conclusion** – 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 a reason for discontinuation. Therefore, long-term studies evaluating the use of biosimilars to monitor adverse events and potential nocebo effects in post-marketing surveillance are still needed.

HEADINGS – Inflammatory bowel diseases, drug therapy. Biological products. Therapeutic equivalency. Biosimilar pharmaceuticals. Review.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the main subtypes of inflammatory bowel disease (IBD), which are chronic conditions of an unclear etiology that lead to lifelong morbidity and decreased quality of life[1,2]. Biologics have revolutionized the management of IBD over the past two decades. Although these drugs are effective and have a good safety profile, they significantly influence treatment-related costs[3,4].

Patents on widely used biologics have recently expired, resulting in a huge opportunity for the development of similar biological medicinal products, the so-called biosimilars[5,6]. A biosimilar is a protein-based drug, developed from recombinant DNA technology, which has a molecular structure and biological properties that are very similar to the original biopharmaceutical product that has already been approved. The food and drug administration defines a biosimilar as "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product"[7].

However, monoclonal antibodies (mAbs) are complex molecules, and although biosimilars have the same amino acid sequence, they are not an exact copy of the original drug, depending on the manufacturing process (e.g., cell line, growth conditions, purification process, and formulation), storage, and transportation. This may reflect differences in glycosylation, phosphorylation, sulfation, and other post-translational modifications, which could affect the efficacy and immunogenicity of the drug[8].

Declared conflict of interest of all authors: **Queiroz NSF** has served as a speaker and advisory board member of Janssen, Takeda and Abbvie. **Saad-Hossne R** has served as a speaker of Janssen, Takeda and Abbvie and advisory board member of Janssen e Pfizer. **Fróes RSB** has served as a speaker of Janssen, Takeda and Abbvie and advisory board member of Janssen. **Penna FGC** has served as a speaker of Janssen, Takeda and Abbvie. **Gabriel SB** discloses no conflicts. **Martins AL** has served as an advisory board member of Janssen. **Teixeira FV** has received fees for serving as a speaker and/or an advisory board member for Abbvie, Janssen and Takeda.

Disclosure of funding: no funding received

[1] Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia, São Paulo, SP, Brasil. [2] Universidade Estadual Paulista (Unesp), Cirurgia Digestiva, Botucatu, SP, Brasil. [3] Gastromed – IBD Clinic, RJ, Brasil. [4] IAG/HC-UFMG, Ambulatório de Intestino e do Grupo de Transplante Hepático, Belo Horizonte, MG, Brasil. [5] Instituto Hospital de Base do Distrito Federal, Brasília, DF, Brasil. [6] GEAF- SESA, Ambulatório de Doenças Inflamatórias Intestinais e Gerência Estadual de Assistência Farmacêutica, Vitória, ES, Brasil. [7] Gastrosaúde – IBD Clinic, Marília, SP, Brasil. Corresponding author: Natália Sousa Freitas Queiroz. E-mail: natalia.freitas@hc.fm.usp.br

The regulatory process required for the market authorization is complex and includes issues regarding manufacturing process; comparability exercise versus the reference product; pharmacokinetic, pharmacodynamic, and efficacy studies; and clinical safety issues. Indeed, safety involves pharmacovigilance and immunogenicity study[9].

When biosimilarity is demonstrated for one of the approved indications of the reference product, approval can be extrapolated to all indications held by the reference biopharmaceutical with a scientific justification[10]. However, global drug regulatory authorities have not yet reached a consensus on the extrapolation of biosimilar indications. For instance, CT-P13, the biosimilar to infliximab, was only tested for rheumatoid arthritis (RA) and ankylosing spondylitis (AS)[11,12] at the time of its approval for CD and UC in Brazil, making this approval a controversial issue as the efficacy and safety of CT-P13 may differ between IBD and RA/AS[13-15].

Studies on the use of biosimilars for IBD are still limited, given that the first biosimilar mAb, CT-P13, was approved only recently (2013 in Europe; 2016 in the United States; 2015 in Brazil[16]). Furthermore, randomized controlled trials comparing reference biologic and biosimilars in IBD are lacking, and the available studies often had a short-term follow-up[17,18]. Moreover, most of available data on biosimilars in IBD are from observational studies from European centers, which described their real-life experience after switching from a reference biologic to a biosimilar[19-21].

Recently, higher-than expected discontinuation rates attributable to "nocebo effect" have been reported in patients with immune-mediated disease who switched from a stable treatment with the originator infliximab to the biosimilar CT-P13[22,23]. However, this effect has not yet been widely explored in IBD population as CD and UC are complex entities with many confounding factors involved in the pathogenesis of disease exacerbation[24].

The aim of this systematic review and meta-analysis was to assess the risk and reasons for drug discontinuation in the IBD population that switched from the originator to biosimilars in real-wolrd studies.

METHODS

The following clinical issues are addressed in the present analysis:

What is the risk of discontinuation of biosimilars following a switch from originator biologics in adult patients with IBD?

What are the main reasons for drug discontinuation?

Is it possible to identify potential nocebo effect as reason for drug discontinuation?

Structured question:
P: patient; I: intervention; C: comparison; O: outcome
P: Adults with IBD
I: Switch from originator biologics to biosimilars
O: Risks of or reasons for discontinuation

The comparison (C) was not specified to not limit the possible unknown comparisons before the search.

The selection of the studies to be included to answer the questions was based on the following eligibility criteria:

1. Elements performing P.I.C.O.
2. Observational studies with analysis of discontinuation
3. At least one treatment switch from an originator therapeutic mAb to a biosimilar thereof
4. Mean follow-up period ≥6 months or three infusions
5. Mean or median duration of treatment using the originator mAb was disclosed and reported as >1-year characterizing maintenance treatment
6. No date restrictions to the search
7. No language restrictions
8. Full text available with the data necessary for the analysis
9. Abstract with extractable data on relevant outcomes

The searched scientific databases were Medline, EMBASE, and Central Cochrane. In addition, a manual search (the references listed in the included studies) and a grey literature search (theses, book chapters, and meeting abstracts) were performed, as necessary.

The search terms used in the databases were as follows – Medline and EMBASE: ((Inflammatory Bowel Disease*) OR (Colitis, Ulcerative) OR (Crohn Disease)) AND (Antibodies, Monoclonal OR Antibodies, Monoclonal, Humanized OR Tumor Necrosis Factor-alpha OR anti-TNF OR Infliximab OR CT-P13 OR Adalimumab OR Golimumab OR Vedolizumab OR Integrins) AND (Biosimilar Pharmaceuticals OR Therapeutic Equivalency OR Biosimilar* OR switch).

Central Cochrane
Inflammatory Bowel Disease AND Biosimilar

The titles, abstracts, or full texts of the retrieved studies were screened for subsequent selection according to the eligibility criteria. The search was stopped by December 31st, 2019. Two authors (NSFQ, FVT) independently reviewed titles/abstracts of studies identified in the search, and excluded those that were clearly irrelevant. All disagreements were solved after a discussion between them.

The selected observational studies were not assessed for risk of biases if they were case series.

The following data were extracted from the selected studies: author's name and year of publication, the main characteristics of the adult patients with IBD, the characteristics and duration of treatment with the originator biologics and biosimilar versions thereof, and the outcomes related to the risk of discontinuation along with the main reasons for discontinuation.

In the selected studies, the outcomes are presented in absolute numbers (number of events). When the available data on a given outcome were common to two or more studies, they were grouped and meta-analyzed to express the overall result of the effect (risk).

Isolated outcomes (reported in only one study) were assessed with regard to their level of importance and may or may not be considered in the results of the present evaluation.

With regard to discontinuation events as a result of the use of biosimilars, the results (effects) are expressed as the difference between before (zero outcomes) and after (number of events) for each event.

Strength of evidence (degree of confidence in the results or effects) was determined for each analyzed outcome and considered the overall risk of biases of the studies included in the analysis, the magnitude and precision of the overall effect, the presence of inconsistencies or indirect evidence, and the presence of publication bias, according to the TABLE 1 and the GRADE methodology in TABLE 2. In addition, quality of evidence was ranked as high, moderate, low, or very low.

The outcomes are presented as forest plots (RevMan 5.3 – Copenhagen, Denmark)[25] associated with the corresponding analysis of quality of evidence (TABLE 2)[26].

TABLE 1. Summary of included studies.

Study	Population	Intervention	Follow-up	Study period
MEDLINE				
Kim NH 2019	IBD (n: 368) (227 CD, 141 UC)	Switched infliximab to CT-P13 (n: 101)	12 months	No information
Chaparro M 2019	IBD (142 CD, 57 UC)	Switched infliximab to CT-P13 (n: 199)	18 months	45 months
Armuzzi A 2019	IBD (n: 810) (452 CD, 358 UC)	Switched infliximab to CT-P13 (n: 155)	392.8±232 days	17±13 infusions
Smits LJT 2019	IBD (n: 83) (57 CD, 24 UC, 2 IBD-U)	Switched infliximab to CT-P13 (n: 83)	12 and 24 months	24 months
Guerra Veloz MF 2018	IBD (n: 98) (67 CD, 31 UC)	Switched infliximab to CT-P13 (n: 98)	12 months	60 months
Bergqvist V 2018	IBD (n: 313) (195 CD, 118 UC)	Switched infliximab to CT-P13 (n: 313)	12 months	53 months
Guerra Veloz MF 2018	IBD (n: 167) (116 CD, 51 UC)	Switched infliximab to CT-P13 (n: 167)	12 months	No information
Høivik ML 2018	IBD (n: 143) (99 CD, 44 UC)	Switched infliximab to CT-P13 (n: 143)	18 months	81 months
Ratnakumaran R 2018	IBD (n: 191) (173 CD, 14 UC, 4 IBD-U)	Switched infliximab to CT-P13 (n: 191)	12 months	55 months
Boone NW 2018	IBD (n: 101) (73 CD, 28 UC)	Switched infliximab to CT-P13 (n: 101)	9 months	42 months
Avouac J 2018	IBD (n: 64) (41 CD, 23 UC)	Switched Infliximab to CT-P13 (n: 64)	9 months	47 months
Schmitz EMH 2018	IBD (n: 133) (88 CD, 45 UC)	Switched infliximab to CT-P13 (n: 133)	12 months	52 months
Smits LJT 2017	IBD (n: 83) (57 CD, 24 UC, 2 IBD-U)	Switched infliximab to CT-P13 (n: 83)	12 months	25 months
Argüelles-Arias F 2017	IBD (n: 98) (67 CD, 31 UC)	Switched infliximab to CT-P13 (n: 98)	12 months	60 months
Guerrero Puente L 2017	IBD (n: 36) (23 CD, 13 UC)	Switched infliximab to CT-P13 (n: 36)	9 months	33 months
Razanskaite V 2017	IBD (n: 143) (118 CD, 14 UC, 4 IBD-U)	Switched infliximab to CT-P13 (n: 143)	12 months	10 infusions
Fiorino G 2017	IBD (n: 547) (313 CD, 234 UC)	Switched infliximab to CT-P13 (n: 97)	6 months	18±14 infusions
Jahnsen J 2017	IBD (n: 56) (37 CD, 19 UC)	Switched infliximab to CT-P13 (n: 56)	6 months	44 months
Kolar M 2017	IBD (n: 74) (56 CD, 18 UC)	Switched infliximab toCT-P13 (n: 74)	14 months	36 months
Smits LJ 2016	IBD (n: 83) (57 CD, 24 UC, 2 IBD-U)	Switched infliximab toCT-P13 (n: 83)	6 months	24 months
Jung YS 2015	IBD (n: 36) (27 CD, 9 UC)	Switched infliximab or adalimumab to CT-P13 (n: 36)	8±3 infusions	No information
EMBASE				
Fischer S 2018 (a)	IBD (n: 114) (72 CD, 42 UC)	Switched infliximab to sb2 (n: 114)	6 months	33 months
Bronswijk M 2018	IBD (n: 401) (285 CD, 116 UC)	Switched infliximab to ct-p13 (n: 361)	6 months	72 months
Fischer S 2018 (b)	IBD (n: 119) (76 CD, 43 UC)	Switched infliximab to sb2 (n: 119)	6 months	33 months
Plevris N 2018	CD (n: 110)	Switched infliximab to ct-p13 (n: 110)	12 months	48 months
Soret PA 2017	IBD (n: 64) (42 CD, 21 UC)	Switched infliximab to ct-p13 (n: 64)	9 months	35 months
Rodríguez Glez GE 2017	IBD (n: 72) (62 CD, 10 UC)	Switched infliximab to bs (n: 72)	12 months	51 months
Bennett KJ 2016	IBD (n: 104) (73 CD, 22 UC, 2 IBD-U)	Switched infliximab to bs (n: 104)	6 months	37 months
ECCO 2019				
Guerra Veloz M 2019	IBD (n: 100) (64 CD, 36 UC)	Switched infliximab to CT-P13 (n: 100)	24 months	58 months
Bhandare AP 2019	IBD (n: 96) (52 CD, 44 UC)	Switched infliximab to CT-P13 (n: 96)	13 months	49 months

References: (a) 38; (b) 40.

TABLE 2. Analysis of quality of evidence of included studies according to the GRADE methogology.

Certainty assessment							Results summary				
							Study event rates (%)			Potential absolute effects	
N. participants (studies) Follow-up	Risk of bias	Inconsistency	Indirect Evidence	Inaccuracy	Publishing Bias	Overall certainty of evidence	BEFORE SWITCH	AFTER SWITCH	Relative effect (95% CI)	Risk BEFORE SWITCH	Risk difference AFTER SWITCH
Discontinuation 6m											
2762 (10 observational studies)	not serious	very serious [a]	not serious	not serious	none	⨁◯◯◯ VERY LOW	0/1381 (0.0%)	111/1381 (8.0%)	**RR 18.30** (7.40 to 45.28)	0 out of 100	**8 more per 100** (from 5 more to 11 more) [b]
Discontinuation 9m											
530 (4 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	0/265 (0.0%)	38/265 (14.3%)	**RR 20.00** (4.88 to 81.98)	0 out of 100	**14 more per 100** (from 10 more to 19 more) [b]
Discontinuation 12m											
3298 (12 observational studies)	not serious	very serious [a]	not serious	not serious	none	⨁◯◯◯ VERY LOW	0/1649 (0.0%)	250/1649 (15.2%)	**RR 34.56** (15.36 to 77.77)	0 out of 100	**14 more per 100** (from 10 more to 18 more) [b]
Discontinuation 18m											
684 (2 observational studies)	not serious	very serious[a]	not serious	serious[c]	highly suspicious publication bias[d]	⨁◯◯◯ VERY LOW	0/342 (0.0%)	96/342 (28.1%)	**RR 65.95** (8.76 to 496.66)	0 out of 1.000	**25 more per 1.000** (from 13 more to 63 more) [b]
Discontinuation 24m											
383 (2 observational studies)	not serious	very serious[a]	not serious	serious[c]	none	⨁◯◯◯ VERY LOW	0/200 (0.0%)	40/183 (21.9%)	**RR 41.53** (5.75 to 300.14)	0 out of 1.000	**21 more per 1.000** (from 7 more to 35 more) [b]
Remission reason											
1832 (7 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	0/916 (0.0%)	35/916 (3.8%)	**RR 11.0** (3.7 to 32.7)	0 out of 100	**4 more per 100** (from 2 more to 5 more) [b]
Reason increased loss of response (disease worsening)											
1024 (3 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	0/512 (0.0%)	11/512 (2.1%)	**RR 8.33** (1.54 to 45.12)	0 out of 100	**2 more per 100** (from 1 more to 4 more) [b]
Reason loss of response											
3076 (13 observational studies)	not serious	serious [e]	not serious	not serious	none	⨁◯◯◯ LOW	0/1538 (0.0%)	125/1538 (8.1%)	**RR 15.39** (6.93 to 34.19)	0 out of 100	**7 more per 100** (from 5 more to 10 more) [b]
Reason loss of adherence											
1542 (8 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	0/771 (0.0%)	31/771 (4.0%)	**RR 8.75** (3.12 to 24.51)	0 out of 100	**4 more per 100** (from 2 more to 6 more) [b]
Reason adverse events											
4042 (17 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	0/2021 (0.0%)	108/2021 (5.3%)	**RR 13.71** (6.85 to 27.43)	0 out of 100	**5 more per 100** (from 4 more to 6 more) [b]

CI: confidence interval; RR: risk ratio. a. Heterogeneity greater than 75%. b. Before and after no events before. c. Wide confidence interval. d. Risk of discontinuity above all other studies (outlier). e. Heterogeneity greater than 50%.

RESULTS

In total, 2,062 studies were retrieved: 336 from Medline, 1,100 from EMBASE, 26 from Central Cochrane, and 600 from grey literature search. After reviewing titles and abstracts against eligibility criteria, 134 studies were selected for further full text access. Of these, 104 studies were excluded for the following reasons: non-switching (27); absence of discontinuation data (32); studies on children (3); review articles (9); absence of data on treatment duration (10); use of drugs other than biosimilars (1); duplicates (15); and others (7) (FIGURE 1).

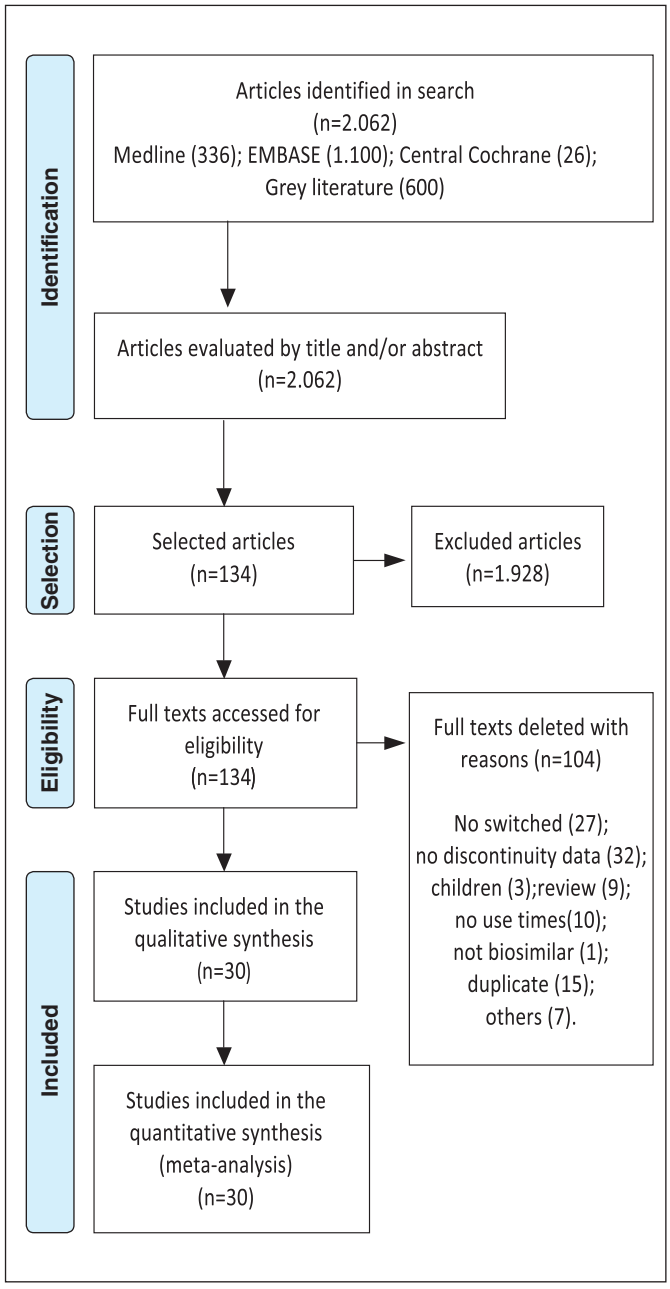

FIGURE 1. Selection of studies recovered in the virtual basis of scientific information.

Therefore, only the cohort of switched patients from the 30 studies included in the present analysis was used, thus making the study design observational[19-23,27-51] (without a comparison group). The analysis included 22 full texts and eight conference abstracts (TABLE 1).

The population included in this analysis comprised 3,594 patients with IBD. The majority of patients had CD, followed by UC. A smaller number of patients had unspecified IBD. The exact distribution of the patients by type IBD cannot be stated because all studies did not have information on the "switched" cohort (TABLE 1).

In the 30 selected studies, the switch from originator biologics to biosimilars occurred as follows: from infliximab to CT-P13 in 26 studies[19-23,27-31,37,39,41,42,46-51] from infliximab to SB2 in 2 studies[38,40], and from infliximab to an unspecified biosimilar in two studies[43,44]. The duration of previous treatments with the originators (before the switch) varied between 2 and 7 years.

The main outcome of the present analysis was biosimilar discontinuation in a follow-up period varying between 6 and 24 months. Separate analyses were conducted for the 6-, 9-, 12-, 18-, and 24-month periods (TABLE 2).

In addition, the reasons for treatment discontinuation were extracted and the reasons that appeared in more than one study were meta-analyzed: remission, disease worsening, loss of response, loss of adherence, and adverse events.

The nocebo effect was explicitly analyzed as a reason for discontinuation in only one study[23], and the frequency of subjective adverse events was low. TABLE 2 presents the adverse events.

The analyses were performed by grouping the results of CT-P13, SB2, and biosimilar unspecified discontinuation. Sensitivity analyses were performed separately using the results of each biosimilar, which showed no significant changes relative to the aggregate results. Thus, each analyzed outcome represents the results, regardless of the biosimilar.

Sensitivity analyses were also performed for loss of response and loss of adherence, with and without the study by Chaparro et al.[48] because of the strong suspicion of publication bias in that study (outlier). Moreover, only the analyses excluding that study were used, because significant differences were found in the results. Therefore, that study[48] was included only in the analysis of discontinuation after 18 months but excluded from the analyses of.

The outcomes are presented as forest plots (RevMan 5.3 – Copenhagen, Denmark)[25] associated with the corresponding quality of evidence analysis (TABLE 2)[26], according to the following sequence:

Risk of discontinuation
a. 6 months
b. 9 months
c. 12 months
d. 18 months
e. 24 months

Reasons for discontinuation
a. Remission
b. Increased loss of response (disease worsening)
c. Loss of response
d. Loss of adherence
e. Adverse events

Risk of discontinuation

After 1,381 patients switched from the originator biologic to

a biosimilar, there was a significant risk of discontinuation of 8% (varying between 5% and 11%) (FIGURE 2) after 6 months. The quality of evidence was very low (TABLE 1).

After 9 months, 265 patients switched from the originator biologic to a biosimilar and there was a significant risk of discontinuation of 14% (varying between 10% and 19%) (supplementary data - FIGURE A). The quality of evidence was low (TABLE 1).

After one year, 1,649 patients switched from the originator biologic to a biosimilar and there was a significant risk of discontinuation of 14% (varying between 10% and 18%) (FIGURE 3).The quality of evidence was very low (TABLE 1).

After 18 months, 342 patients switched from the originator biologic to a biosimilar, and there was a non-significant risk of discontinuation of 25% (varying between 13% and 63%) (supplementary data - FIGURE B). The quality of evidence was very low, with high suspicion of publication bias (TABLE 1).

And finally, after two year, 183 patients switched from the originator biologic to a biosimilar, and there was a significant risk of discontinuation of 21% (varying between 7% and 35%) (FIGURE 4). The quality of evidence was very low (TABLE 1).

Reasons for discontinuation

After 916 patients switched from the originator biologic to a biosimilar, there was a significant risk of discontinuation due to remission in 4% of cases (varying between 2% and 5%) (FIGURE 5). The quality of evidence was low (TABLE 1). On the other hand, disease worsening was a significant risk of discontinuation in 2% of cases (varying between 1% and 4%) (FIGURE 6), after 512 patients switched from the originator biologic to a biosimilar. The quality of evidence was low (TABLE 1). The loss of response was a significant risk of discontinuation in 7% of cases (varying between 5% and 10%) (FIGURE 7), after 1,538 patients switched from the originator biologic to a biosimilar, with very low quality of evidence (TABLE 1). Loss of adherence was responsible for discontinuation in 4% of cases (varying between 2% and 6%) (supplementary data - FIGURE C), after 771 patients switched from the originator biologic to a biosimilar. The quality of evidence was very low (TABLE 1). Finally, adverse events was a significant risk for discontinuation in 5% of cases (varying between 4% and 6%) (supplementary data - FIGURE D), with low quality of evidence (TABLE 1).

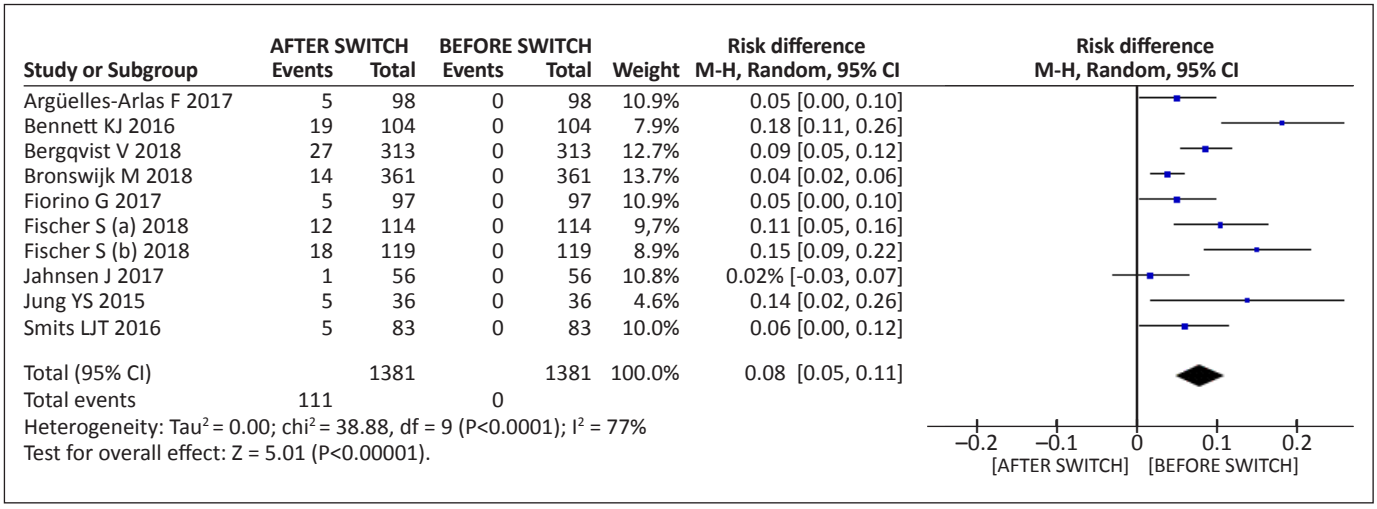

FIGURE 2. Number of discontinuation events after 6 months. (a) reference 38; (b) reference 40.

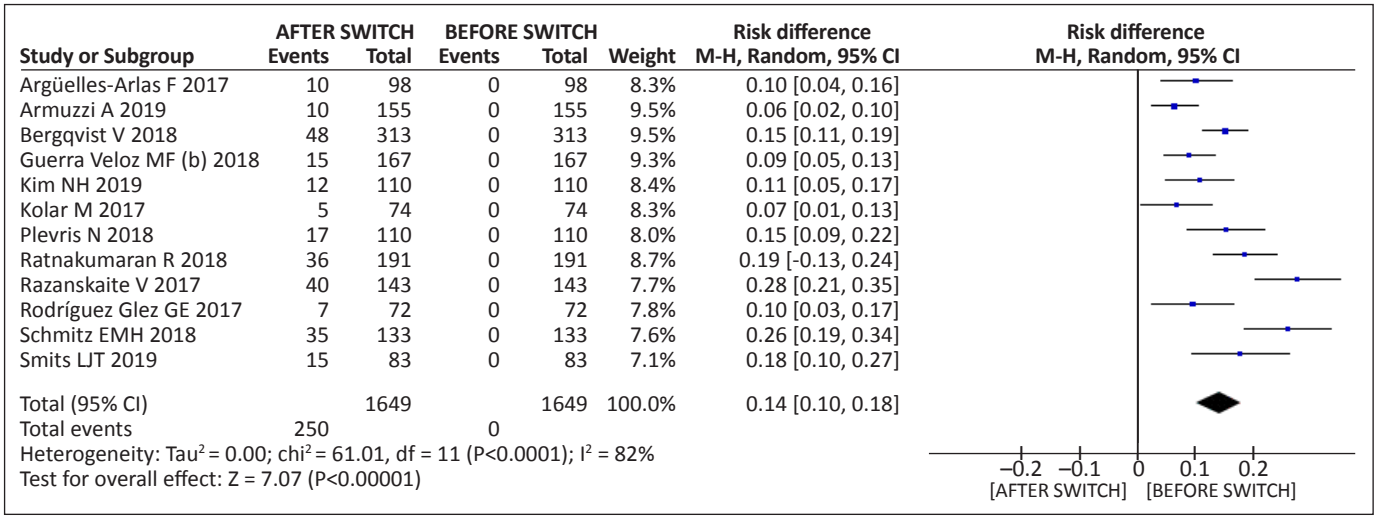

FIGURE 3. Number of discontinuation events after 12 months.

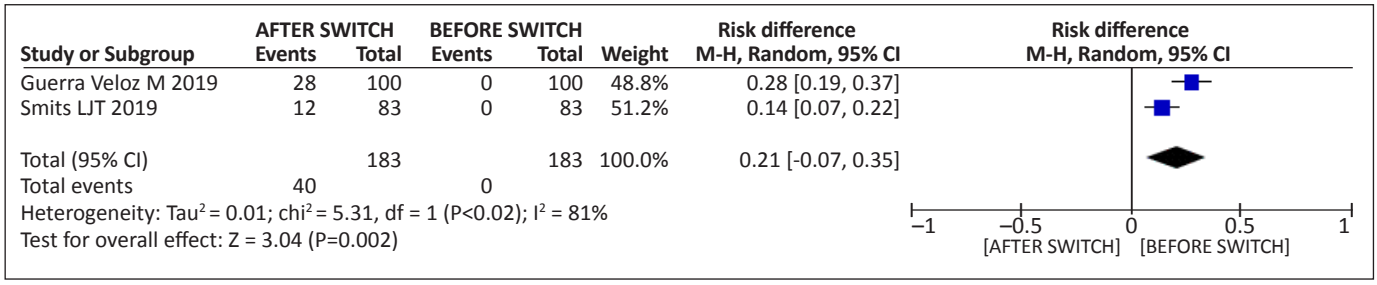

FIGURE 4. Number of discontinuation events after 24 months.

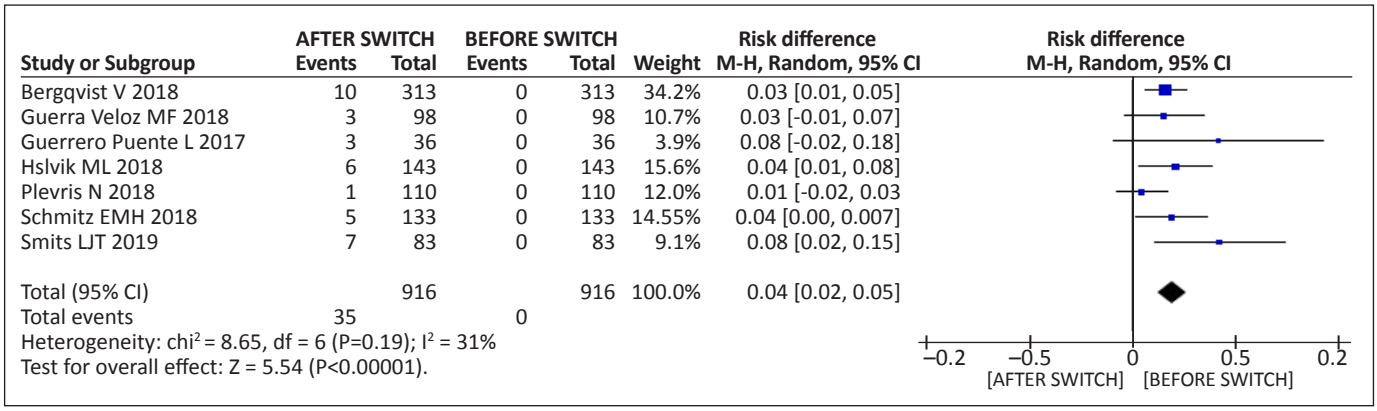

FIGURE 5. Number of discontinuation events due to remission.

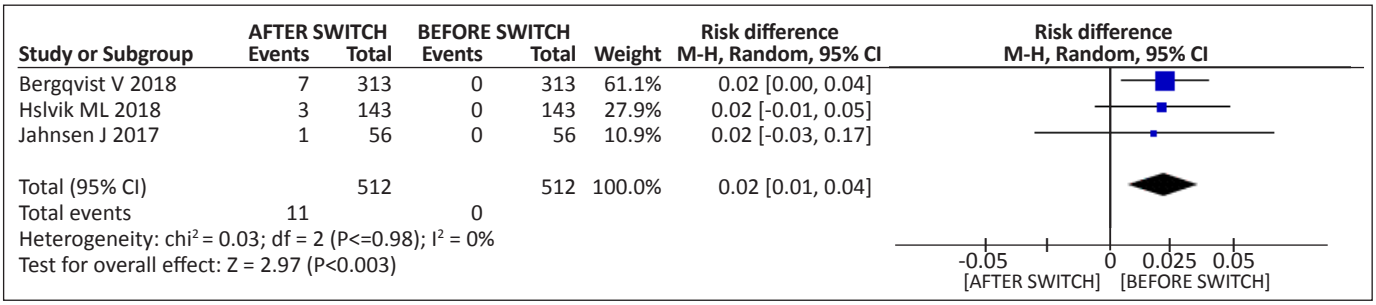

FIGURE 6. Number of discontinuation events due to disease worsening.

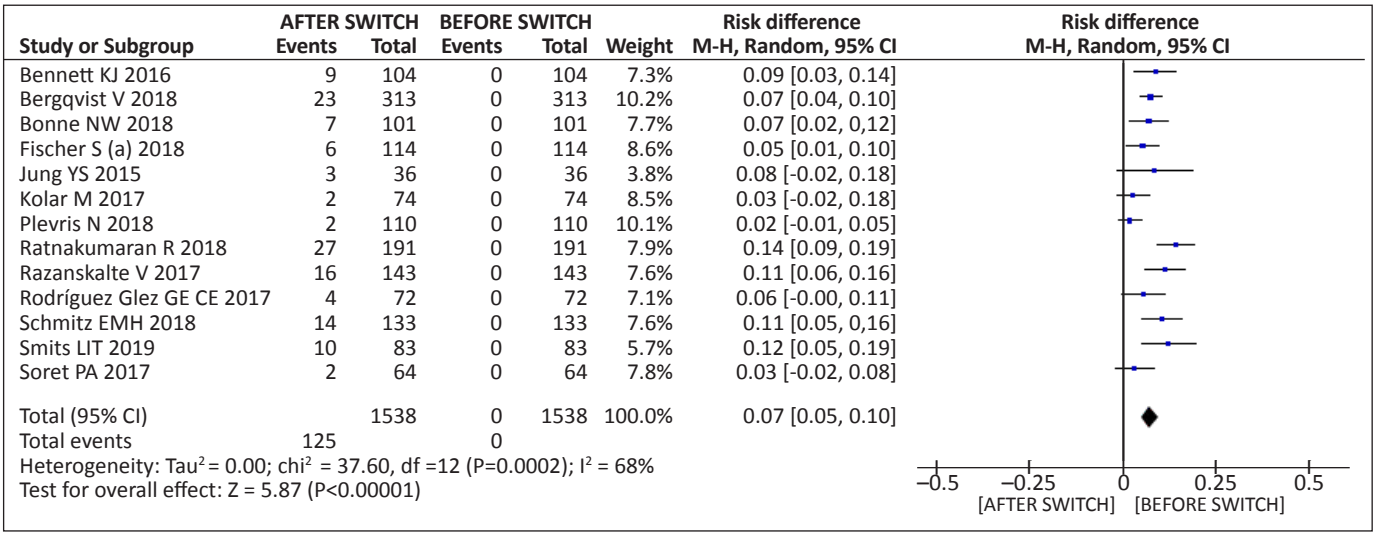

FIGURE 7. Number of discontinuation events due to loss of response. (a) reference 38.

DISCUSSION

To our knowledge, this is the first systematic review to evaluate studies including a switch from a reference to all mAb biosimilar in patients with IBD to date. The risk of discontinuation of biosimilars after a switch from originator biologics in patients with IBD increased with increasing treatment duration, with the discontinuation rates being 8%, 14%, and 21% after 6, 12, and 24 months, respectively. The main reasons for discontinuation and respective risks in ascending order were: 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, which indicated that there was no clear reason for discontinuation.

The yearly discontinuation rate for reference infliximab in historic cohorts after the first year of therapy has been reported as 7%–13%[24,52,53]. Like those in biosimilar cohorts, the main reasons for discontinuation of reference infliximab in historic cohorts were loss of response and adverse events. Although these data indicate similar efficacy and safety profile for biosimilars and reference infliximab, it is important to emphasize that the populations in those analyses are very heterogeneous, making any direct comparison impossible.

A recently published switch study, which was included in our analysis, demonstrated a higher rate of discontinuation among switched patients than among non-switched patients receiving reference infliximab[54]. Although this switch study was considered an outlier in the present analysis, it was one of the few switch studies that included a control cohort. Moreover, there was no clear objective reason for this discontinuation rate in the biosimilar cohort, thus suggesting the presence of the "nocebo" effect. We personally corresponded with the author of this switch study[54] to retrieve missing data on the switching program in their cohort (Chaparro M, personal communication, April 2019). The author revealed that patients were only informed by the health care provider regarding the switch, and no previous preparation and support group were available.

The nocebo effect is the opposite of the placebo effect. In the context of biologic switching studies, the nocebo effect relates to a perceived worsening of symptoms or loss of response induced by switching to the biosimilar due to unexplained but nevertheless existing patients' concerns about the clinical value and effect of a drug. In some cases, disease worsening can be misinterpreted, leading to drug suspension[55].

Although many observational real-world studies have demonstrated that switching to biosimilars in IBD population is safe and effective[37,56,57], the rationale for switching is only related to cost savings. In this context, non-medical switching should be performed following appropriate discussion between the IBD team (physicians, nurses, pharmacists) and patients and according to institutional board recommendation[58]. Furthermore, it has been proposed that a managed educational switching program empowering patients may increase confidence avoiding nocebo effects[23].

Although non-medical drug switching in patients with IBD is not commonly quantified or reported objectively, it may have a negative impact on patients' disease perception, the so-called nocebo effect. Boone et al.[23] showed an overall nocebo response of 12%, which did not differ between patients with IBD and those with rheumatological diseases.

Studies have reported that a switch from a reference biologic to a biosimilar has no significant impact on the immunogenicity, safety, and efficacy of the drug[37,56,57]. Therefore, on the basis of these results, reverting to initial treatment after a switch from a reference biologic to a biosimilar is not expected to be a frequent event.

However, in a study by Reuber and Kostev conducted in Germany in 2019, almost a third of the patients who switched from originator biologics to biosimilars reverted to their reference drug treatment[59]. Unfortunately, the authors did not specify the reasons for this reversal. Therefore, further long-term studies specifically addressing subjective symptoms as reasons for drug discontinuation are required to better characterize the nocebo effect.

The introduction of biosimilars should not be guided by economic concerns alone. Monitoring a change in therapeutic strategy requires strict pharmaco vigilance and investigation of the reasons behind the discontinuation of a biosimilar product and the switch back to an originator. In addition, monitoring of data on safety and efficacy, both at the individual and population levels, is required.

In a study by Boone et al.[23], loss of financial gain in the transition to a biosimilar was not influenced solely by the nocebo effect. The percentage of patients not willing to switch (14.4%), the nocebo effect rate (13%), and the operational costs of the switch led to an overall 37% reduction in costs and a 50% price reduction. These data contribute to our recommendation that a switch should be based on collaborative decision-making, benefiting individual patients, rather than on systematic non-medical decisions that can compromise safety and treatment adherence.

IBD is a complex disease, which may be worsened due to subjective symptoms. Furthermore, many factors influence this disease worsening and trigger flares such as irritable bowel syndrome symptoms, anti-tumor necrosis factor trough levels, and anti-drug antibodies (ADAs). Most of the studies included in the present analysis did not disclose information about disease activity at the moment of switch, and only a few studies described trough levels before and after switch. Results from NORSWITCH study revealed no differences in terms of ADA formation between patients switched to CT-P13 and all study patients or the subgroups of patients stratified for disease[18]. However, the clinical development program of SB2, a biosimilar of infliximab, has shown a slight excess of ADA positivity, which was higher in the RA trial[60]. This result leads to great concern and uncertainty as many other biosimilars are under development and, during the approval process, clinical trials have less regulatory emphasis[61]. By the end of this search, no study assessing discontinuation rates following a switch from adalimumab originator to its biosimilar was identified. But it is important to emphasize that biosimilar drug development is an evolving situation and real world data evaluating efficacy and safety of emerging biosimilars will soon be available.

To conclude if drug persistence is affected by the nocebo effect or other parameters, further accumulation of evidence is highly recommended from switching studies, involving patients with IBD who are in deep remission, as shown by clinical, laboratory, and endoscopic parameters, as well as a non-switching population with the same characteristics. These studies should assess nocebo responses as a measured outcome. It would also be interesting to assess whether a managed switching program could affect those outcomes. Moreover, long-term studies on biosimilar use are still needed to monitor adverse events in post-marketing surveillance.

Our meta-analysis has some limitations. First, the evaluation of the nocebo effect was not possible, since only one study specifically analyzed this effect in the switch from a reference to a biosimilar. Second and more importantly, the level of evidence was low or very low for all studied variables due to the heterogeneity of the studies

included as well as the large confidence interval of relative risk. This reflects the need for well-conducted prospective studies to address the question regarding the switch in biological therapy for IBD.

In conclusion, our systematic review and meta-analysis demonstrated an increasing risk of discontinuation over time of 8%, 14%, and 21% at 6, 12, and 24 months, respectively. Patient symptoms leading to drug discontinuation were infrequently reported, and the nocebo effect was clearly assessed in only one[23] of the included papers.

Authors' contribution

All authors collected the data and conceived, designed and performed the analysis. The paper was written by Queiroz NSF and Teixeira FV. Final revision was done by Queiroz NSF, Saad-Hossne R and Teixeira FV.

Orcid

Natália Sousa Freitas Queiroz: 0000-0003-2857-0825.
Rogerio Saad Hossne: 0000-0002-8166-0304.
Renata de Sá Brito Fróes: 0000-0003-3256-4698.
Francisco Guilherme Cancela e Penna: 0000-0002-2338-5367.
StefaniaBurjack Gabriel: 0000-0002-8455-1701.
Adalberta Lima Martins: 0000-0002-0273-5743.
Fabio Vieira Teixeira: 0000-0002-8915-7279.

Queiroz NSF, Saad-Hossne R, Fróes RSB, Penna FGC, Gabriel SB, Martins AL, Teixeira FV. Taxas de descontinuação do tratamento após a troca de um biológico originador por um biossimilar em pacientes com doenças inflamatórias intestinais: revisão sistemática e metanálise. Arq Gastroenterol. 2020;57(3):232-43.

RESUMO – **Contexto** – Os biológicos revolucionaram o tratamento da doença inflamatória intestinal (DII). Ademais, esses medicamentos influenciaram os custos relacionados ao tratamento. Tal aumento significativo nos gastos com o tratamento motivou desenvolvimento dos biossimilares. **Objetivo** – Esta revisão sistemática e metanálise objetivou avaliar a taxa de descontinuação de medicamentos na população com DII que foi submetida à troca do biológico originador para um biossimilar, em estudos observacionais que abordaram possíveis razões para a descontinuação do tratamento. **Métodos** – Tendo como base de dados Medline (via PubMed), EMBASE, Cochrane Library e resumos de congressos médicos, foram rastreados artigos com relatos de troca de um biológico originador por um biossimilar, com acompanhamento pós-troca de no mínimo 6 meses ou três infusões. Todas as informações disponíveis sobre as taxas de descontinuação foram avaliadas. **Resultados** – Foram incluídos no total 30 estudos observacionais, envolvendo 3.594 pacientes com DII. Vinte e seis estudos relataram uma mudança do infliximabe para CT-P13, dois estudos envolveram uma mudança para o SB2, e as informações sobre a troca não estavam disponíveis em dois estudos. As taxas de descontinuação foram de 8%, 14% e 21% aos 6, 12 e 24 meses, respectivamente. Os principais motivos para a descontinuação do medicamento e seus respectivos riscos foram: agravamento da doença (2%), remissão (4%), perda de adesão (4%), eventos adversos (5%) e perda de resposta (7%). A qualidade da evidência variou de baixa a muito baixa, dependendo do resultado analisado. Os sintomas subjetivos que levaram à descontinuação do medicamento foram relatados com pouca frequência, e o efeito nocebo foi claramente avaliado em apenas um dos artigos incluídos. **Conclusão** – As taxas de descontinuação após a mudança para um biossimilar em pacientes com DII aumentam com o tempo. No entanto, não foi possível confirmar o efeito nocebo como motivo da descontinuação. Portanto, ainda são necessários estudos em longo prazo avaliando o uso de biossimilares para monitorar eventos adversos e potenciais efeitos nocebo na vigilância pós-comercialização.

DESCRITORES – Doenças inflamatórias intestinais, tratamento farmacológico. Produtos biológicos. Equivalência terapêutica. Medicamentos biossimilares. Revisão.

REFERENCES

1. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. Inflamm Bowel Dis. 2006;12 (Suppl 1):S3-9.
2. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007;369:1627-40.
3. van der Valk ME, Mangen MJJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. Gut. 2014;63:72-9.
4. Cohen RD, Thomas T. Economics of the use of biologics in the treatment of inflammatory bowel disease. Gastroenterol. Clin. North Am. 2006;35:867-82.
5. Calo-Fernandez B, Martinez-Hurtado JL. Biosimilars: company strategies to capture value from the biologics market. Pharmaceuticals (Basel). 2012;5:1393-408.
6. McCamish M, Woollett G. Worldwide experience with biosimilar development. MAbs 2011;3:209-17.
7. US Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Rockville, MD: US Food and Drug Administration 2012. [Internet]. Available from: https://www.biologicsblog.com/content/uploads/2016/09.
8. Schiestl, M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011;29:310-2.
9. Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. Nat Rev Gastroenterol Hepatol. 2017;14:22-31.
10. Feagan BG, Lam G, Ma C, Lichtenstein GR. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. Aliment Pharmacol Ther. 2018;49:31-40.
11. 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. Ann Rheum Dis. 2013;72:1605-12.
12. 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. Ann Rheum Dis. 2013;72:1613-20.

13. Feagan BG, Choquette D, Ghosh S, Gladman DD, Ho V, Meibohm B, et al. The challenge of indication extrapolation for infliximab biosimilars. Biologicals. 2014.
14. Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? AAPS J. 2014;16:22-6.
15. Vande Casteele N, Sandborn WJ. IBD: Indication extrapolation for anti-TNF biosimilars. Nat. Rev. Gastroenterol Hepatol. 2015;12:373-4.
16. ANVISA homepage [Internet]. [Access 2019 December]. Available from: http://portal.anvisa.gov.br
17. 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;393:1699-707.
18. 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;389:2304-16.
19. Smits LJT, Derikx LAAP, de Jong DJ, Boshuizen RS, van Esch AAJ, Drenth JPH, Hoentjen F. Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease patients: A prospective observational cohort study. J Crohn's Colitis. 2016;10:1287-93.
20. 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. Inflamm Bowel Dis. 2017;23:233-43.
21. Kolar M, Duricova D, Bortlik M, Hruba V, Machkova N, Mitrova K, et al. Infliximab biosimilar (RemsimaTM) in therapy of inflammatory bowel diseases patients: Experience from one tertiary inflammatory bowel diseases centre. Dig Dis. 2017;35:91-100.
22. 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. Semin. Arthritis Rheum. 2018;47:741-8.
23. 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. Eur J Clin Pharmacol. 2018;74:655-61.
24. Ben-Horin S, Chowers Y. Review article: Loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther. 2011;33:987-95.
25. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
26. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017;87:4-13.
27. Bergqvist V, Kadivar M, Molin D, Angelison L, Hammarlund P, Olin M, et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. Therap Adv Gastroenterol. 2018;11:1-13.
28. Guerra Veloz MF, Morón JMV, Jiménez MB, Manrique HP, Delgado TV, Laria LC, Pérez BM, et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: results of a multicenter study after 12 months. Rev Esp Enferm Dig. 2018;110:564-70.
29. Høivik ML, Buer LCT, Cvancarova M, Warren DJ, Bolstad N, Moum BA, Medhus AW. Switching from originator to biosimilar infliximab - real world data of a prospective 18 months follow-up of a single-centre IBD population. Scand J Gastroenterol. 2018;53:692-9.
30. Ratnakumaran R, To N, Gracie DJ, Selinger CP, O'Connor A, Clark T, et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scand J Gastroenterol. 2018;53:700-7.
31. Schmitz EMH, Boekema PJ, Straathof JWA, van Renswouw DC, Brunsveld L, Scharnhorst V, et al. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study. Aliment Pharmacol Ther. 2018;47:356-63.
32. Smits LJT, Grelack A, Derikx LAAP, Jong DJ, van Esch AAJ, Boshuizen RS, et al. Long-term clinical outcomes after switching from Remicade®to biosimilar CT-P13 in inflammatory bowel disease. Dig Dis Sci. 2017;62:3117-22.
33. Arguëlles-Arias F, Veloz MFG, Amarillo RP, Vilches-Arenas A, Laria LC, Pérez BM, et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: 12 months results. Eur J Gastroenterol Hepatol. 2017;29:1290-5.
34. Guerrero Puente L, Flores EI, Benítez JM, Medina RM, Rodríguez IS, Melero PA, et al. Evolution after switching to biosimilar infliximab in inflammatory bowel disease patients in clinical remission. Gastroenterol Hepatol. 2017;40:595-604.
35. 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. J Crohns Colitis. 2017;11:690-6.
36. Jahnsen J, Kaasen Jørgensen K. Experience with biosimilar infliximab (Remsima®) in Norway. 2017;35:83-90.
37. Jung YS, Park DI, Kim YH, Lee JH, Seo PJ, Cheon JH, Kang HW, Kim JW. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. J Gastroenterol Hepatol. 2015;30:1705-12.
38. Fischer S, Klenske E, Schmitt H, Vitali F, Hirschmann S, Koch F, et al. Effectiveness, immunogenicity, safety and pharmacoeconomic aspects following a switch from reference infliximab to the biosimilar SB2 in inflammatory bowel disease patients: a 6 months prospective cohort study. United European Gastroenterol J. 2018;6(8 Suppl): A135–A747.
39. Bronswijk M, Moens A, Lenfant M, Tops S, Compernolle G, Assche GV, et al. Evaluating efficacy, safety and pharmacokinetics after switching from infliximab originator to biosimilar ct-p13: results from a large Tertiary referral center. United European Gastroenterol J. 2018:6:A135-A747.
40. Fischer S, Klenske E, Schmitt H, Vitali F, Hirschmann S, Koch F, et al. Clinical outcomes and immunogenicity analysis over 6 months following a switch from originator infliximab (Remicade®) to the biosimilar SB2 (Flixabi®) in inflammatory bowel disease patients. J Crohn's Colitis. 2018;12:S416.
41. Plevris N, Jones GR, Jenkinson PW, Lyons M, Chuah CS, Merchant LM, et al. Implementation of CT-P13 via a managed switch programme in Crohn's disease: 12-month real-world outcomes. Dig Dis Sci. 2019;64:1660-7.
42. Soret PA, Chaparro M. Efficacy and safety of switching from reference infliximab to biosimilar infliximab in patients with inflammatory bowel disease: first French experience. [Article in En, Spanish]. J Crohn's Colitis. 2017;11:S318-S319.
43. Rodríguez Glez GE, Díaz Hernández L, Morales Barrios JA, Vela González M, Tardillo Marín CA, Viña Romero V, et al. Efficacy, safety and economic impact of the switch to biosimilar of infliximab in inflammatory bowel disease patients in clinical practice: results of one year. Journal of Crohn's & Colitis. 2017;11(Suppl 1):S402. https://doi.org/10.1093/ecco-jcc/jjx002.753
44. Bennett KJ, Heap GA, Hawkins SAT. Prospective evaluation of the safety and efficacy of switching stable patients with Inflammatory bowel disease from Remicade™ to biosimilar infliximab (IFX). Gut. 2016;65 (Suppl 1):A146. doi: 10.1136/gutjnl-2016-312388.263
45. Guerra Veloz M, Jiménez MB, Delgado TV, Laria LC, Pérez BM, Amarillo RP, et al. Long-term follow-up of switching from original infliximab to infliximab biosimilar: real-world data. Therap Adv Gastroenterol. 2019;12:1756284819858052. doi: 10.1177/1756284819858052.
46. Bhandare AP, Crooks B, Nigam GB, Limdi LK. P337 Switching from originator infliximab to CT-P13: single-centre experience from the UK. J Crohn's Colitis. 2019;13:S538. doi.org/10.1093/ecco-jcc/jjy222.461
47. Kim NH, Lee JH, Hong SN, Yoon H, Kang HW, Lee SH, et al. Long-term efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. J Gastroenterol Hepatol. 2019;14645.
48. 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. J Crohn's Colitis. 2019;13:1380-6.
49. Armuzzi A, Fiorino G, Variola A, Manetti N, Fries W, Orlando A, et al. The PROSIT Cohort of Infliximab Biosimilar in IBD: A Prolonged Follow-up on the Effectiveness and Safety Across Italy. Inflamm Bowel Dis. 2019;25:568-79.
50. Smits LJT, van Esch AAJ, Derikx LAAP, Boshuizen R, Jong DJ, Drenth JPH, Hoentjen F. Drug survival and immunogenicity after switching from Remicade to biosimilar CT-P13 in inflammatory bowel disease patients: Two-year follow-up of a prospective observational cohort study. Inflamm Bowel Dis. 2018;25:172-9.
51. Veloz MFG, Argüelles-Arias F, Laria LC, Pérez BM, Roldan AB, Amarillo RP, et al. Loss of efficacy and safety of the switch from infliximab original to infliximab biosimilar (CT-P13) in patients with inflammatory bowel disease. World J Gastroenterol. 2018;24:5288.
52. Seminerio JL, Loftus EV, Colombel JF, Thapa P, Sandborn WJ. Infliximab for Crohn's disease: The first 500 patients followed up through 2009. Dig Dis Sci. 2013;58;797-806.
53. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Assche GV, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: Results from a single-centre cohort. Gut. 2009;58:492-500.
54. Pillai N, Dusheiko M, Maillard MH, Rogler G, Brüngger B, Bähler C, Pittet VEH, Swiss IBD Cohort Study Group. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. J CrohnsColitis. 2019;13:744-54.

55. Planès S, Villier C, Mallaret M. The nocebo effect of drugs. Pharmacol Res Perspect. 2016;4:e00208.
56. Gonczi L, Gecse KB, Vegh Z, Kurti Z, Rutka M, Farkas K, et al. Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort. Inflamm Bowel Dis. 2017;23:1908-15.
57. 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. J Crohns Colitis. 2016;10:133-40.
58. 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. J Crohn's Colitis. 2017;11:26-34.
59. Reuber K, Kostev K. Prevalence of switching from two anti-TNF biosimilars back to biologic reference products in Germany. Int J Clin Pharmacol Ther. 2019;57:323-8.
60. European Medicines Agency European Medicine Agency. Flixabi. Committee for medicinal products for human use (CHMP). CHMP assessment report [EMA/CHMP/272283/2016]. London: EMA. 2016. Available from: http://www. ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_asses.
61. Danese S, Peyrin-Biroulet L. To switch or not to switch: That is the biosimilar question. Nat Rev Gastroenterol Hepatol. 2017;14:508-9.

SUPPLEMENTARY DATA

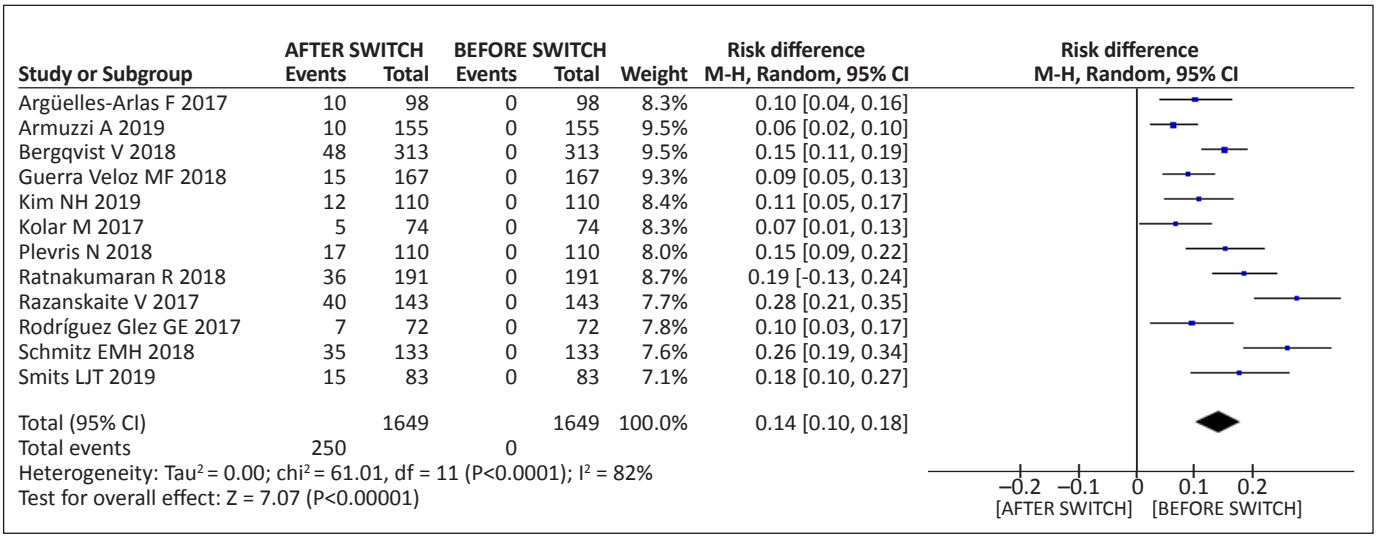

FIGURE A. Number of discontinuation events after 9 months.

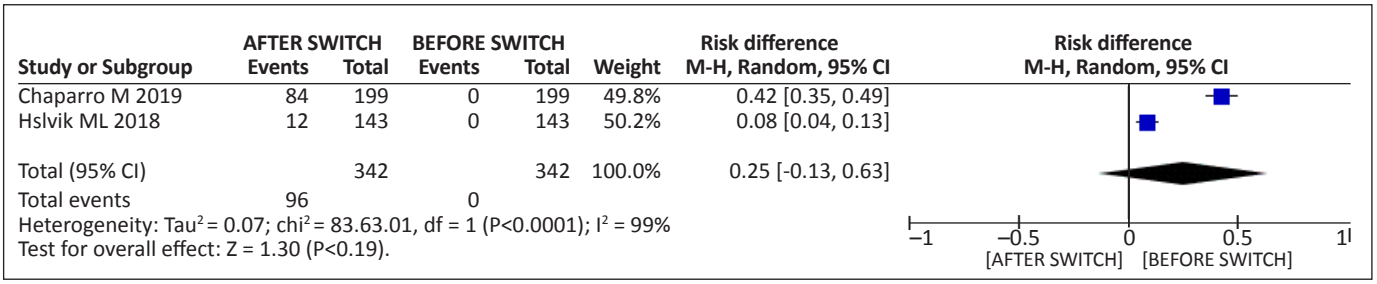

FIGURE B. Number of discontinuation events after 18 months.

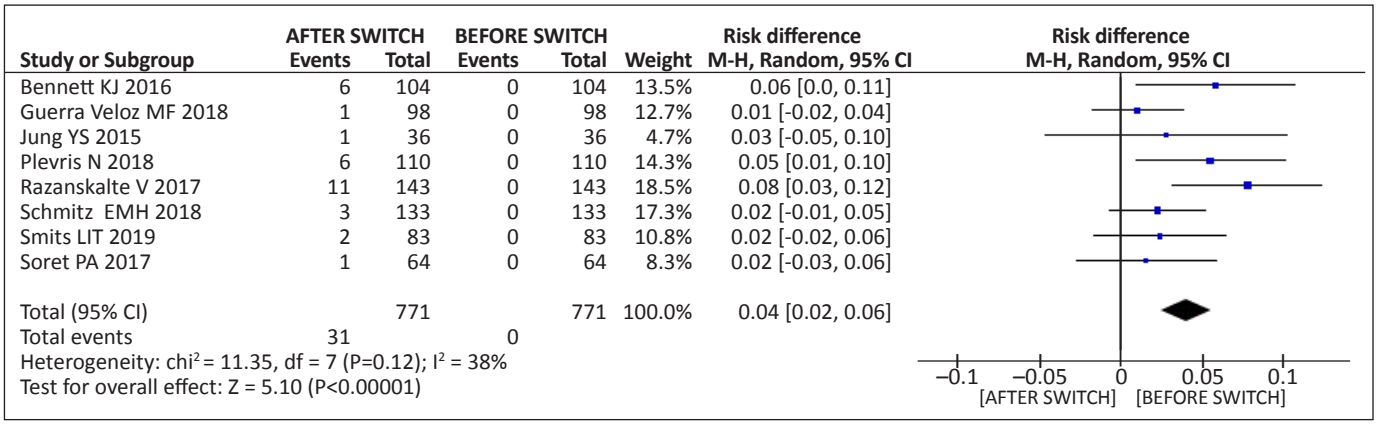

FIGURE C. Number of discontinuation events due to loss of adherence.

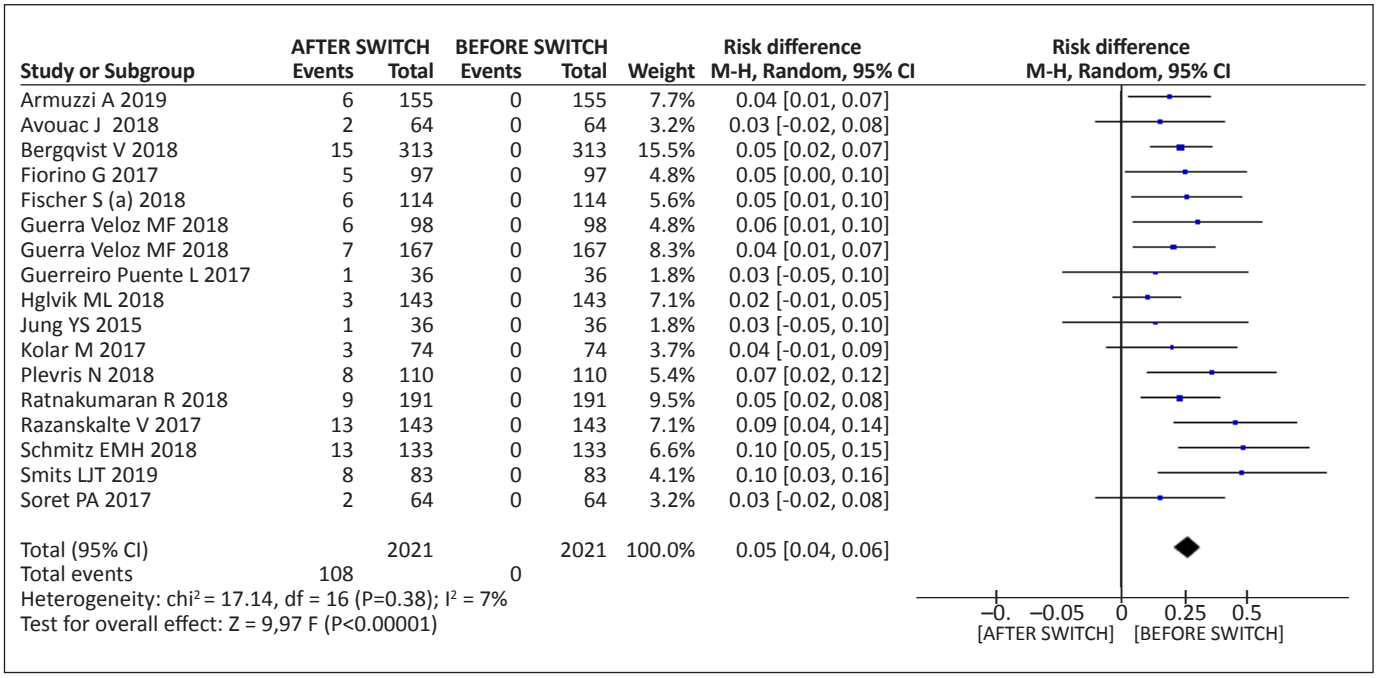

FIGURE D. Number of discontinuation events due to adverse events.