



ARTICLE

Safety and clinical efficacy of the double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases (SCESICS): A multicenter cohort study

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Abstract

Data regarding double switching from originator infliximab (IFX) to IFX biosimilars in inflammatory bowel diseases (IBDs) are lacking. The purpose of this study was to evaluate the safety and efficacy of switching from originator IFX to CT-P13 and subsequently to SB2 (double switch) in patients with IBD. Patients undergoing IFX-double switch in eight Centers in Lombardy (Italy) from

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November 2018 to May 2019 were retrospectively analyzed. The IFX discontinuation rate, incidence and type of adverse events (AEs), and clinical remission rate were recorded. A comparison with a control group of patients with IBD single-switched from originator IFX to CT-P13 was performed, before and after an inverse probability of treatment weighting (IPTW)-based propensity score analysis. Fifty-two double-switched patients with IBD were enrolled. The 24- and 52-week proportions of patients continuing on IFX therapy following the second switch (CTP13 → SB2) were 98% (95% confidence interval [CI] 94%–100%) and 90% (95% CI 81%–99%), respectively. Four patients experienced a total of five AEs, all graded 1–3 according to Common Terminology Criteria for Adverse Events (CTCAE). No infusion reactions were observed. The 24-week and follow-up end clinical remission rates following the second switch were 94% and 88%, respectively. No differences were observed in the safety and efficacy outcomes by comparing the double-switch group with a single-switch group of 66 patients with IBD; all these results were confirmed by IPTW-adjusted analysis. The study suggests both the safety and efficacy of the double switch from originator IFX to CT-P13 and SB2 in patients with IBD is maintained. This strategy may be associated with potential cost implications.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Biosimilars reduce the direct costs of therapy and facilitate access to high-cost therapies to patients. Data show that switching from originator infliximab to infliximab biosimilars (CT-P13 or SB2) is safe and effective. Few data are available on the outcomes of double switch (from biological originator to a first biosimilar and then to a second biosimilar), and caution has been expressed by the European Crohn's and Colitis Organization (ECCO) and the Italian Group for the study of inflammatory bowel disease (IBD; IG-IBD).

WHAT QUESTION DID THIS STUDY ADDRESS?

The study was aimed to compare the effectiveness and safety of single and double switch of infliximab (IFX) in patients with IBDs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

No differences were found in clinical response and remission as well as adverse events between either single or double IFX switch. Data were consistent with the safety profile of IFX.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Double switch strategy is safe and effective in IBD. These data assume high relevance in terms of cost-savings strategies.

INTRODUCTION

Biosimilars, defined by the European Medicines Agency as “medicines highly similar to another biological medicine already marketed in the European Union (the so-called ‘reference medicine’)” constitute a relevant opportunity to save on the costs of biological therapy in patients with multiple medical conditions. In 2015, the

first infliximab (IFX) biosimilar (CT-P13) was licensed and has since entered the EU market for all the indications of the reference drug, including inflammatory bowel diseases (IBD; Crohn's disease [CD], and ulcerative colitis [UC]). Since 2015, CT-P13 has progressively been prescribed in the European Union for both naïve patients (e.g., patients never treated with IFX), and in IFX-experienced patients, thus replacing originator IFX

(a practice defined as “switch”). In the last few years, several observational and randomized studies have been published, supporting the safety and clinical effectiveness of CT-P13 in patients with IBD, both IFX-naïve and experienced¹⁻³ ones. Specifically, switching from originator IFX to CT-P13 has been supported by a double-blind noninferiority trial (the NOR-SWITCH study), which included patients with several autoimmune diseases.⁴ In this study, switching from originator IFX to CT-P13 was found not to be inferior to continued treatment with originator IFX according to a prespecified 15% noninferiority margin.⁴ It should be underlined, however, that the NOR-SWITCH study was not powered to show noninferiority in individual diseases.

More recently, a second IFX biosimilar SB2 (Samsung Bioepis, Incheon, Republic of Korea) has been developed and entered the market. SB2 was approved in the United States on April 21, 2017, and has also been approved in Norway, Liechtenstein, Iceland, and Australia, in addition to having been approved in the European Union and Korea. SB2 and reference IFX (INF; Remicade, Janssen Biotech, Horsham, PA) have been shown to have comparable structure, function, pharmacokinetic parameters, immunogenicity, and safety.⁵⁻¹⁰ The clinical efficacy of SB2 and that of IFX in patients with rheumatoid arthritis have been found to be comparable in a phase III equivalence study.⁵ Of note, switching from originator IFX (Remicade) to SB2 has reportedly been safe and effective up to 78 weeks in a recent randomized study in patients with rheumatoid arthritis.⁹

At present, only one study assessed the safety and effectiveness of switching for nonmedical indications between the two IFX biosimilars. CT-P13 and SB2, or double switching (originator IFX → CT-P13 → SB2).¹¹ In this study, the subgroup of 24 patients who underwent multiple switches showed similar safety and effectiveness of SB2 as compared with data reported for IFX originator and CT-P13. Specifically, in the SB2 arm, the rate of adverse events (AEs) was 16.7% with a 4.2% rate of drug withdrawal for AEs.

These data are relevant because the practice of switching to more than one biosimilar is presently not recommended by scientific societies, as concerns exist regarding the potential immunogenicity and increasing risk to develop side effects.^{12,13} Despite these recommendations, several IBD centers in Lombardy have decided to switch patients to SB2 for budget-related reasons, because the latter drug is currently cheaper than both originator IFX and CT-P13 in this region.

In the present study, we retrospectively collected data on the efficacy and safety of patients with IBD double-switched from originator IFX to CT-P13 and subsequently to SB2 in Lombardy and then followed up for at least

6 months. These data were compared with the data from a comparable cohort of patients single-switched from originator IFX to CT-P13.

METHODS

Study population and data collection

The data from all the patients with IBD double-switched from originator IFX to CT-P13 (first switch) and subsequently to SB2 (second switch) were retrospectively analyzed. The patients single-switched from originator IFX to CT-P13 were recruited during the same period and were analyzed as controls. The data were collected from eight centers in Lombardy (Italy), patients being eligible if they were 18+ years old and had an established diagnosis of UC or CD with at least a 6-month follow-up. A minimum follow-up of 6 months after the second switch was also required for enrollment in the first group. The exclusion criteria were: diagnosis of IBD unclassified, presence of a concurrent malignancy, history of opportunistic infections, history of severe medical or psychiatric comorbidities, and current pregnancy or breast-feeding.

The following baseline clinical variables were recorded: sex, age at diagnosis and at enrollment, smoking status, disease type (CD or UC), combo therapy after switch, disease duration, and duration of each IFX therapy (originator drug, CT-P13 and SB2). All AEs were graded according to version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute.¹⁴

The protocol was approved by the local ethics committee of each participating center, and it was performed according to the Helsinki Declaration. All the patients gave their written informed consent about their participation in this study.

Outcome measures

The primary objective was the evaluation of the safety of the double-switch strategy. The end points for this purpose included the number and details of AEs, the rate of AEs over time, and the percentage of patients forced to stop IFX because of AEs over time after SB2 start were recorded. The secondary objectives were: (1) to assess the efficacy of the double-switch strategy, defined as the rate of clinical remissions at week 24 and at follow-up end, and the rate of loss of response over time (including the need of optimization); (2) to assess any difference in safety and efficacy outcomes between the double-switch group and the control group of single-switched patients, both before and

after propensity score-based analysis; and (3) to find any baseline clinical predictive factors of safety and efficacy.

Clinical remission for UC was considered as a partial Mayo score, a specific disease activity index for UC, less than 2 with no partial score greater than 1 and no rectal bleeding, whereas response was a 30% and three-point reduction of the partial Mayo score.¹⁵ Clinical remission from CD was considered a Crohn's Disease Activity Index (CDAI) less than 150 or a Harvey-Bradshaw Index (HBI) less than or equal to 4, whereas response was taken as a 100-point or three-point reduction of CDAI or HBI, respectively.^{16,17}

Loss of response was defined as an initial response to CT-P13, followed by a diminished or less durable response over time leading to drug discontinuation or optimization.^{18,19} IFX optimization was performed by either increasing dosage (10 mg/kg) or reducing the infusion intervals (every 4–6 weeks).

Statistical analysis

The categorical variables are described as absolute frequency and percentage. The continuous variables with normal distribution are described as median \pm SD, whereas the continuous variables without normal distribution are given as median and range. Survival curves were obtained with the nonparametric Kaplan-Meier estimator. The Cox proportional hazards model was used to investigate the association between the rate of IFX discontinuation over time (both because of AEs and loss of response) and the double-switch or single-switch strategy; for the analysis, the hazard ratio was referred to the double-switch strategy. The Cox proportional hazards model was also applied to find any clinical baseline predictors of IFX discontinuation in the double-switch group. A propensity score-adjusted analysis was then performed to reduce any bias caused by imbalanced covariates and to confirm the validity of analysis. Propensity scores (the conditional probabilities of being in the double or single-switch group) were first calculated using a binary regression model based on the following variables: sex, age at diagnosis, disease type, combination therapy, smoking status, disease duration, and IFX therapy duration at the single or double switch. Then, the patients' data were weighted by Inverse Probability of Treatment Weighting (IPTW) approach; weights were stabilized by trimming at the first and 99th percentiles. The balance of each variable between the unweighted (original cohort) and the weighted (pseudo-cohort obtained by weighting) groups was verified by computing the standardized differences. Absolute standardized differences of less than 10% are considered optimal, whereas absolute

standardized differences of less than 20% are considered adequate. The IPTW-adjusted binary logistic regression was computed to compare the clinical remission rate at week 24 between double- and single-switched patients. IPTW-adjusted Cox regression analysis was performed for the estimation of the effect of double switch toward IFX discontinuation and loss of response rates over time. Differences in the frequency of overall and type-specific AEs, and in the rate of clinical remission at week 24 and at follow-up end between the double-switch and single-switch strategy was evaluated using the χ^2 or the Fisher's exact tests. All the analysis was carried out by computer software IBM SPSS Statistics (release 25; IBM Corporation, USA) and STATA (release 14.1; StataCorp, USA).

RESULTS

Between November 2018 and May 2019, a total of 52 patients with IBD previously switched from originator IFX to CT-P13 underwent a second switch to SB2. All data were available about the 52 enrolled patients (63% men, mean age at diagnosis 41 ± 11 years, 75% CD, and 25% UC) toward the final analysis. Main indications for IFX therapy were disease severity (50%) and steroid-dependency (25%). All patients were switched for economic reasons. The clinical baseline data of the double-switched patients are reported in Table 1 (left column). At the time of the second switch, all the patients were initially kept on the same ongoing IFX-therapeutic scheme. Specifically, if any previous optimization had been performed (i.e., IFX every 6 or 4 weeks, or IFX 10 mg/kg every 8 weeks), this was maintained. The single-switched-control group included 66 patients with IBD, whose clinical baseline data are reported in Table 1 (middle column). The double-switch group had a shorter disease duration and a short IFX therapy duration before the switch compared to the single-switch group. Prior to propensity score matching with IPTW, the patients' characteristics were unbalanced between the two groups for smoking status, disease duration, and duration of IFX therapy at single or double switch. Propensity scoring with IPTW allowed for a good balancing of variables between the two groups, by assuring that the absolute standardized differences were less than 0.1 for six variables and less than 0.2 for one variable (Figure S1).

Safety analysis

In the double-switched patients, the median total duration of IFX biosimilar therapy was 113 weeks (range 39–214),

TABLE 1 Clinical and demographic features of the 52 patients enrolled in the study

Clinical parameters	Double switch n = 52	Single switch n = 66	p value ^a
Sex, male, n (%)	33 (64)	45 (68)	0.591
CD/UC, n (%)	39/13 (75/25)	47/19 (71/29)	0.646
Perianal disease	11 (21)	10 (15)	0.470
CD location, ^b n (%)			
L1 (ileal)	8 (15)	7 (10)	0.579
L2 (colonic)	5 (9.6)	10 (15)	0.417
L3 (ileocolonic)	25 (48)	28 (42)	0.579
L3 + L	1 (2)	3 (4.5)	0.629
UC extension, ^b n (%)			
E2 (left-sided)	5 (9.6)	5 (7.5)	0.747
E3 (extensive)	8 (15)	14 (21)	0.240
Age at diagnosis, mean ± SD - years	28 ± 12	27 ± 11	0.520
Disease duration, mean ± SD - years	13 ± 8	17 ± 10	0.031
Smoking status at double switch, yes, n (%)	11 (21)	8 (12)	0.185
Combo therapy with AZA at the double- or single-switch, n (%)	7 (14)	11 (17)	0.631
IFX therapy duration at the double- or single-switch, median (range) - months	53 (10–212)	31 (5–648)	<0.001
Follow-up time after the double- or single-switch, median (range) - months	16 (3–39)	37 (3–58)	<0.001

Abbreviations: AZA, azathioprine; CD, Crohn's disease; IFX, infliximab; UC, ulcerative colitis.

^aChi-square or Fisher's exact test.

^bAccording to the Montreal classification.

which included 69 weeks (range 6–174) on CT-P13 and 40 weeks (range 8–48) on SB2 therapy.

The 24- and 52-week overall proportions of patients continuing on IFX therapy over time were 98% (95% confidence interval [CI] 94%–100%) and 90% (95% CI 81%–99%), respectively (Figure 1). After starting on SB2, four patients (7.6%) experienced a total of five AEs, all graded 1–3. No grade 4–5 treatment-related AEs were observed, with particular reference to neoplasia or death. Noteworthy, no infusion reactions occurred after the

second switch. Observed AEs among the double-switched patients were mostly classified as dermatological, infectious, or articular, including purpuric rash of the lower limbs, worsening of pre-existing psoriasis, herpes zoster of the torso, recurrent genital herpes, and one case of de novo arthralgia that warranted rheumatological advice. A detailed list of AEs and clinical characteristics of patients experiencing AEs are detailed in Table 2 (left column) and Table 3. AEs led to SB2 discontinuation in two (4%) patients (suffering from recurrent genital herpes and cutaneous purpuric lesions) and resolved after drug withdrawal. According to the Kaplan-Meier survival curve, the proportions of patients not discontinuing IFX therapy because of AEs over time were 98% (95% CI 94%–100%) at week 24 and 96% (95% CI 91%–100%) at week 52. No differences in the IFX discontinuation rates due to AEs over time were observed between double-switched and single-switched patients based on Cox regression analysis: nonadjusted (hazard ratio [HR] 0.7, 95% CI 0.1–4.1, $p = 0.73$; Figure 2) and IPTW-adjusted (HR 1.0, 95% CI 0.1–8.1, $p = 0.98$). Moreover, no differences in the frequency of overall and type-specific AEs were found between the double-switch and single-switch strategy (Table 2, right column). Finally, no clinical parameters were found to predict the rate of IFX discontinuation for AEs over time in the double-switched patients' group.

Effectiveness

The median follow-up period after the second switch (i.e., SB2 initiation) was 72 weeks (24–171). Only two patients were treated with a combination of SB2 and azathioprine, both being already on combination therapy before the second switch. At week 24 following the second switch, clinical remission was maintained in 49 of 52 patients (94%). Among the three patients not in clinical remission at week 24, one had clinical response with optimized IFX (optimization being performed already during therapy with CT-P13) and was subsequently maintained on IFX. The other two patients were discontinued from therapy before week 24 because of permanent loss of response despite optimization. No differences in the clinical remission rates at week 24 were observed when comparing the double-switch and the single-switch strategies (adjusted OR 1.3, 95% CI 0.3–6.2, $p = 0.73$). After week 24, IFX (SB2) dose optimization through the shortening of infusion rates was necessary for four patients: one patient then recovered response and was therefore considered in clinical remission at the end of follow-up; and three patients permanently lost response despite optimization after week 24. Thus, 46 of 52 patients (88%) were in clinical remission at the end of follow-up. Overall, SB2 was stopped for loss of response

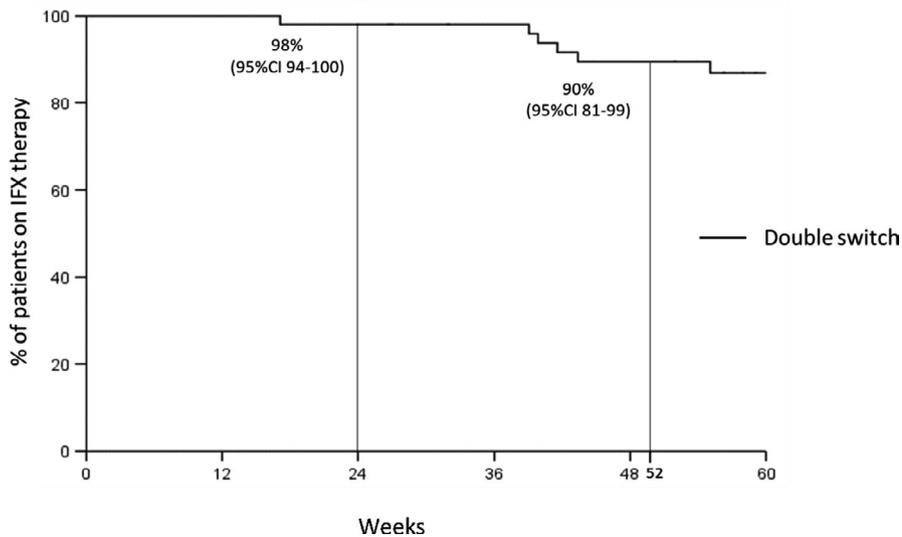


FIGURE 1 Overall proportion of double-switched patients continuing infliximab therapy over time. CI, confidence interval; IFX, infliximab

TABLE 2 Overall frequency of adverse events in the double switch or single switch groups

	Double switch <i>n</i> = 52	Single switch <i>n</i> = 66	<i>p</i> value ^a
Total AE, <i>n</i> (%)	5 (9.6)	8 (12.4)	0.772
Infusion reactions, <i>n</i> (%)	0	5 (7.2)	0.066
Cutaneous, <i>n</i> (%)	2 (3.8)	1 (1)	0.582
Infectious, <i>n</i> (%)	2 (3.8)	0	0.192
Articular, <i>n</i> (%)	1 (1.9)	1 (0.5)	1.000
Neurological, <i>n</i> (%)	0	1 (0.5)	1.000
Immuno-mediated, <i>n</i> (%)	1 (1.9)	1 (0.5)	1.000
Neoplastic, <i>n</i> (%)	0	0	NA
Other, <i>n</i> (%)	0	1 (0.5)	1.000
Total SAEs (CTCAE 4–5), <i>n</i> (%)	0	0	NA
Stop for AEs, <i>n</i> (%)	2 (3.8)	4 (6.1)	0.693

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; SAE: serious adverse event.

^aChi-square or Fisher's exact test.

in five patients. According to the Kaplan-Meier survival curve, the proportions of patients maintaining the clinical response over time (including patients recovering their response after optimization) were 98% (95% CI 94–100) at week 24 and 91% (95% CI 83–99) at week 52 (Figure 3). After comparison with the single-switched control group, no differences in the loss of clinical response rates were found according to the Cox regression analysis of both the original cohort (HR 0.7, 95% CI 0.3–1.7, $p = 0.40$) and the IPTW-weighted cohort (HR 0.9, 95% CI 0.2–3.4, $p = 0.86$). No clinical parameters were found to predict clinical remission at week 24 and at the end of follow-up after the second switch. In our little experience, we found no

variation in biochemical markers and fecal calprotectin; moreover, we did not observe any hospitalizations or IBD-related abdominal surgeries during the follow-up after the second switch.

DISCUSSION

The introduction of monoclonal antibody (mAb) biosimilars represent a major milestone in the treatment of patients with IBD, as they significantly reduce the direct cost of biological therapies and improve therapy access for a larger population of patients, especially in countries where reimbursement policies discourage the use of high-cost therapies.¹³ Several concerns about switching from the originator mAb to one relevant biosimilar have been raised in the recent past,^{20–24} especially as efficacy, safety (i.e., increase in infusion reactions), and immunogenicity are concerned. Data from one randomized controlled trial (the NOR-SWITCH trial)⁴ and from large observational cohort studies on patients with IBD^{1,2,25–27} clearly demonstrate that switching from the originator drug to one of the relevant biosimilars (CT-P13, or SB2) is not associated with any significant reduction in efficacy or increased risk of adverse events or development of antidrug antibodies.

Despite the current data supporting a single switch from originator IFX to a biosimilar, limited data are available on the outcomes of a second switch from a biosimilar to another. Thus, the European Crohn's and Colitis Organization (ECCO) and the Italian Group for the study of IBD (IG-IBD) suggest caution with double-switching.^{12,13}

However, the switch among two biosimilars of the same mAbs is often justified by economic reasons (i.e., the need to save money for other highly expensive therapies). This practice is defined as nonmedical switching,

TABLE 3 Clinical and demographic features of double-switched patients experiencing AEs

Patient no.	Patient #1	Patient #2	Patient #3	Patient #4
Sex	Female	Female	Female	Female
Age (years)	68	55	31	39
Smoke yes/no	No	No	No	Yes
CD/UC extension and behavior ^a	CD L3 B3p	CD L2 B1	CD L3 B3p	UC E2
Extraintestinal manifestations	Peripheral arthropathy	Ankylosing spondylitis/iridocyclitis	Psoriasis/eritema nodosum	None
Anti-TNF therapy naïve/experienced	Naïve	Naïve	Experienced	Naïve
Type of AEs	Dermatological/infectious Herpes zoster	Infectious/articular Genital herpes simplex De novo arthralgia	Dermatological worsening psoriasis	Immuno-mediated Purpura of lower limbs
Time from second switch to AEs (months)	4	3	3	9
Outcomes	Complete resolution after antiviral therapy. Continued therapy with SB2.	Stop for AEs. Complete resolution after withdrawal	Stop for secondary LOR	Stop for AEs. Complete resolution after withdrawal.

Abbreviations: AE, adverse event; Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; LOR, loss of response; UC, ulcerative colitis.

^aAccording to the Montreal classification.

because the decision of switching is not driven by medical reasons and often is independent from the clinician's will. Because in Italy the drug reimbursement to the hospitals is performed by the National Health System, saving costs is currently regarded as a relevant issue.

In this retrospective longitudinal cohort study, we have analyzed a cohort of patients with IBD who underwent nonmedical double-switch between CT-P13 and SB2, after the first switch from the reference product (Remicade). We have compared the efficacy and safety outcomes with those of a control cohort of patients who underwent a single switch from the originator drug to a biosimilar. Notably, no differences were found in terms of clinical response and clinical remission both at week 24 and at the end of the follow-up period. The loss of response rate at the end of follow-up was around 15%, which is the expected rate of secondary loss of response with any IFX therapy in patients with IBD,² with no statistically significant differences in the two study groups.

The rate of AEs was relatively small and consistent with the safety profile of IFX, in general, and with the relevant biosimilars.²⁸ No infusion reactions were reported in the double-switch group, and no statistically significant differences in terms of any AE were found compared to the single-switch group. In addition, the AEs reported in the double-switch group were numerically even lower than those in the control group. The IPTW propensity score analysis confirmed these findings.

The data emerging from this study assume high relevance in terms of cost-savings strategies. In countries where the national health system is completely public, reducing drug costs translates into improved access of high-cost treatments to a larger proportion of patients. In a recent tender for the supply of biological drugs launched by ARCA Lombardy in 2017, the costs of CT-P13 and SB2 were € 234/vial and € 119.90/vial, respectively. Assuming an 8-week maintenance regimen for a 70-Kg man with no need for optimization, switching from CT-P13 to SB2 would translate into an annual saving of € 2720/year. The total saving on 52 patients would be € 144,160 per year. This sum would be sufficient to treat another 50 patients with the same economic resources.

Our study has several strengths: specifically, the involvement of tertiary referral centers in Lombardy, already collaborating in an IBD regional network (Gruppo di Studio per le Malattie Infiammatorie Intestinali [GSMII]), and sharing protocols for the diagnosis and treatment of IBD, allowed for the collection of highly homogeneous data, including AE reporting.

This study has some limitations. First, the total number of patients was relatively small to reveal any rare event that may occur as a result of double switch. Second, we could not collect any data about drug trough levels and

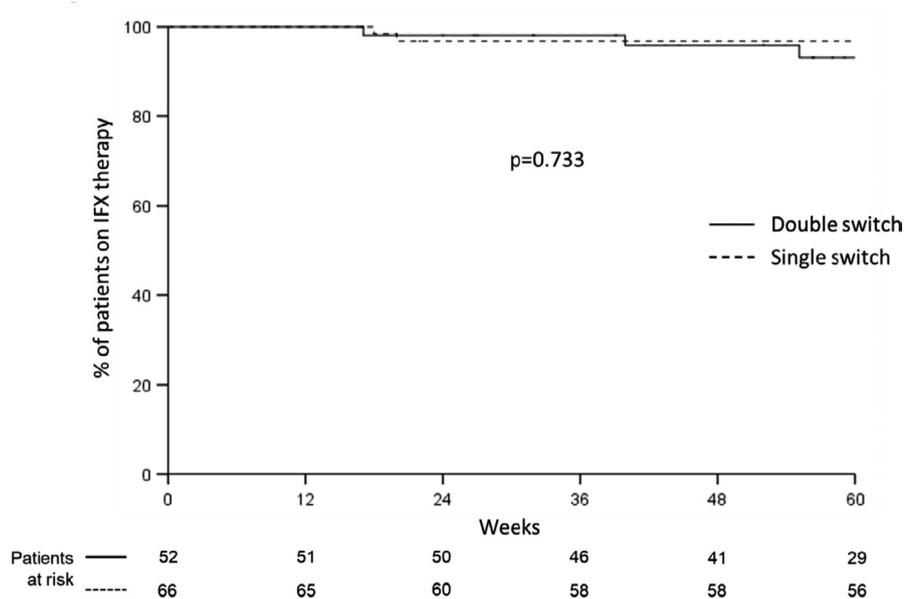


FIGURE 2 Proportion of patients discontinued from infliximab because of adverse events over time, according to a double-/single-switch strategy. IFX, infliximab

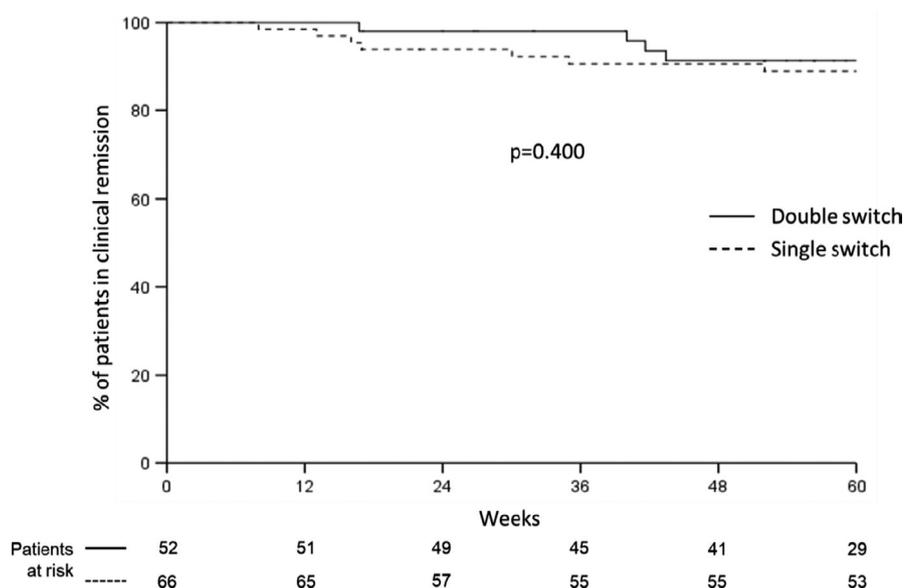


FIGURE 3 Proportion of patients maintaining the clinical response (included optimized cases) over time, according to a double-/single-switch strategy

antidrug antibody formation, because this was a retrospective study and proactive therapeutic drug monitoring is not reimbursed in Italy and not yet routinely recommended by European guidelines.^{29,30} Nevertheless, in our experience, we found no clinically relevant signals of immunogenicity-related events (such as loss of response or infusion reactions). Third, there were some statistically significant differences in terms of baseline characteristics, such as prior IFX therapy duration, although these differences did not significantly impact the results of the IPTW propensity score analysis.

In conclusion, our data suggest that nonmedical double-switching of biosimilars is effective and safe in patients with IBD. Further data on immunogenicity are

needed. These data need to be confirmed in larger prospective studies.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.M., N.P.O.S., G.F., and F. Caprioli wrote the manuscript; N.P.O.S., S.M., F. Caprioli, and G.F. designed the research; A.F., A.R., B.M., V.C., C.R., F.M., L. Pastorelli, F.

Cavallaro, C.G., G.L., L. Pirola, P.I., F.S.C., N.P.O.S., L.F., A.C., A.A., G.E.T., and M.V. performed the research; S.M., G.F., and F. Caprioli analyzed the data; G.E.T. and M.V. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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