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Mahmmod, S.; Schultheiss, J.P.D.; Bodegraven, A.A. van; Dijkstra, G.; Gilissen, L.P.L.; Hoentjen, F.; ... ; Fidder, H.H.

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Outcome of Reverse Switching From CT-P13 to Originator Infliximab in Patients With Inflammatory Bowel Disease

Shaden Mahmmod, MD,[*,a] Johannes P D Schultheiss, MD,[*,a] Ad A van Bodegraven, MD, PhD,[†] Gerard Dijkstra, MD, PhD,[‡] Lennard P L Gilissen, MD, PhD,[§] Frank Hoentjen, MD, PhD,[¶] Maurice W M D Lutgens, MD, PhD,[‖] Nofel Mahmmod, MD,[**] Andrea E van der Meulen–de Jong, MD, PhD,[††] Lisa J T Smits, MD,[¶] Adriaan C I T L Tan, MD, PhD,[‡‡] Bas Oldenburg, MD, PhD,[*] and Herma H Fidder, MD, PhD[*]

From the [*]Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, the Netherlands
[†]Department of Gastroenterology and Hepatology, Zuyderland Medisch Centrum, Sittard, the Netherlands
[‡]Department of Gastroenterology and Hepatology, University Medical Centre Groningen, Groningen, the Netherlands
[§]Department of Gastroenterology and Hepatology, Catharina Ziekenhuis, Eindhoven, the Netherlands
[¶]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, the Netherlands
[‖]Department of Gastroenterology and Hepatology, Elisabeth TweeSteden Ziekenhuis, Tilburg, the Netherlands
[**]Department of Gastroenterology and Hepatology, St. Antonius Ziekenhuis, Nieuwegein, the Netherlands
[††]Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, the Netherlands
[‡‡]Department of Gastroenterology and Hepatology, Canisius-Wilhelmina Ziekenhuis, Nijmegen, the Netherlands
[a]These authors contributed equally.

Address correspondence to: Herma H. Fidder, MD, PhD, Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (h.h.fidder@umcutrecht.nl).

Background: Patients suffering from inflammatory bowel diseases (IBD) and treated with originator infliximab are increasingly being switched to biosimilars. Some patients, however, are "reverse switched" to treatment with the originator. Here we assess the prevalence of reverse switching, including its indication and outcomes.

Methods: In this retrospective multicenter cohort study, data on patients with IBD from 9 hospitals in the Netherlands were collected. All adult patients with IBD were included if they previously had been switched from originator infliximab to the biosimilar CT-P13 and had a follow-up time of at least 52 weeks after the initial switch. The reasons for reverse switching were categorized into worsening gastrointestinal symptoms, adverse effects, or loss of response to CT-P13. Drug persistence was analyzed through survival analyses.

Results: A total of 758 patients with IBD were identified. Reverse switching was observed in 75 patients (9.9%). Patients with reverse switching were predominantly female (70.7%). Gastrointestinal symptoms (25.5%) and dermatological symptoms (21.8%) were the most commonly reported reasons for reverse switching. In 9 patients (12.0%), loss of response to CT-P13 was the reason for reverse switching. Improvement of reported symptoms was seen in 73.3% of patients after reverse switching and 7 out of 9 patients (77.8%) with loss of response regained response. Infliximab persistence was equal between patients who were reverse-switched and those who were maintained on CT-P13.

Conclusions: Reverse switching occurred in 9.9% of patients, predominantly for biosimilar-attributed adverse effects. Switching back to originator infliximab seems effective in patients who experience adverse effects, worsening gastrointestinal symptoms, or loss of response after switching from originator infliximab to CT-P13.

Key Words: inflammatory bowel disease, Crohn disease, ulcerative colitis, biologic therapy, infliximab, biosimilars, anti-TNF-alpha

Introduction

The treatment of inflammatory bowel diseases (IBD) is notoriously cumbersome but has improved considerably with the introduction of anti-tumor necrosis factor alpha monoclonal antibodies, such as infliximab and adalimumab.[1]

In June 2013, the European Medicines Agency approved the first biosimilar monoclonal antibody drug, CT-P13, for the treatment of several immune-mediated inflammatory diseases, including IBD.[2] Per definition, biosimilar drugs or biosimilars are biological drugs that have a biochemical structure highly similar but not identical to that of the originator and are believed to have an efficacy and safety profile similar to that of the originators (therapeutic equivalence).[3]

The European Crohn's and Colitis Organization has stated that prescribing biosimilars and switching from originators to biosimilars in patients with IBD is acceptable, provided that patients are well informed and adequately monitored.[4] Hence, it has become common practice in many European countries to switch originator infliximab to a biosimilar infliximab in patients with IBD, primarily because of economic incentives.[5]

Although infliximab biosimilars by definition have an effectiveness and safety profile similar to that of their originators, it has been reported that at 52 weeks postswitch, 7.5% to 29% of patients discontinued treatment because of, eg, secondary loss of response, new adverse effects, or a return to treatment with originator infliximab (ie, reverse switching).[6-13]

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It has recently been postulated that treatment failure after a nonmedical switch can be partly ascribed to the nocebo effect. Whether this is the case, and whether it may be worthwhile to switch patients back to originator infliximab, is presently unclear.[14,15]

Currently, reverse switching is not recommended because of a lack of clinical and scientific evidence.[4] One study recently showed that it is at least safe to switch patients from CT-P13 maintenance to originator infliximab, yet none of the patients were reverse-switched.[16] Thus, data on reverse switching still need to be extended and corroborated to elucidate its practical consequences.

We aimed to assess the prevalence of and the specific reasons for reverse switching from the biosimilar CT-P13 to originator infliximab within 52 weeks after an initial switch from originator infliximab to CT-P13 in patients with IBD. Furthermore, we sought to establish the clinical effectiveness of reverse switching.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective, multicenter cohort study was performed in 9 hospitals in the Netherlands. Adult patients diagnosed with Crohn disease or ulcerative colitis who were switched from originator infliximab to CT-P13 with a minimum postswitch follow-up of 52 weeks, regardless of infliximab (dis)continuation, were eligible for inclusion. All patients were informed with a letter regarding the switch to biosimilar infliximab. Consent for the switch was obtained by the treating physician.

Procedure

Data on patients from 4 tertiary referral centers and 5 general hospitals were collected. In all patients, originator infliximab was switched to CT-P13 between May 2015 and December 2017 according to the local hospital's protocol. Data were extracted from electronic medical record systems. Patient-specific data included sex, IBD diagnosis, Montreal classification, smoking status, age at switch and diagnosis, duration of originator infliximab treatment, and reasons for infliximab discontinuation. Reasons for infliximab discontinuation were categorized as loss of response, adverse effects, long-term clinical remission, or miscellaneous. If available, fecal calprotectin and infliximab trough levels were collected during CT-P13 use and up to 3 and 6 months, respectively, before switching to CT-P13 or after reverse switching to originator infliximab. Infliximab-neutralizing antibodies were measured only in patients with infliximab trough levels <1.0 mg/L.

Reasons for reverse switching were categorized as adverse effects, worsening gastrointestinal symptoms, or proven loss of response to CT-P13. Adverse effects were further categorized as dermatological, rheumatological, neurological, infectious, or psychological adverse effects, fatigue, or an allergic reaction. Loss of response was defined as an increase of gastrointestinal symptoms and an elevated fecal calprotectin level >250 μg/g or macroscopic signs of disease activity on endoscopic examination.

Statistical Analysis

Baseline characteristics were displayed as medians with interquartile ranges (IQRs) for continuous variables and as counts with percentages for categorical variables. Categorical variables were compared using the χ^2 test or the Fisher exact test when appropriate. Normality was tested for all continuous variables. Because all continuous variables had a nonparametric distribution, the Mann-Whitney *U* test was used for analyses of continuous variables.

Kaplan-Meier curves were constructed from the moment of switching to CT-P13 to establish the univariable differences in drug persistence between patients who were reverse-switched and those who were maintained on CT-P13. Patients who were still on infliximab therapy at the moment of data capture, discontinued infliximab therapy for remission, or who were lost to follow-up after 1 year were censored. An event was defined as discontinuation of infliximab therapy for loss of response, adverse effects, or miscellaneous.

Univariable and multivariable Cox proportional hazards models were fitted to assess hazard ratios (HRs) for infliximab discontinuation in the whole cohort. For all covariables, the proportional hazards assumptions were checked. Time-dependent covariates were used if categorical variables violated the proportional hazards assumption.[17] Continuous variables that violated the proportional hazards assumption were transformed or removed from the model if transformation was insufficient. We treated CT-P13/originator infliximab use as a time-varying covariate. All models were clustered by hospital to adjust for similarities between patients treated at the same hospital.

Paired analyses of infliximab trough levels was done by the Friedman rank-sum test and the Wilcoxon signed-rank test. Posthoc pairwise comparisons after the Friedman rank-sum test were adjusted for by the Bonferroni correction.

A 2-sided *P* value <0.05 or a 95% confidence interval (CI) excluding the 1.0 were considered statistically significant. Statistical analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

This study was carried out with the approval of and in accordance with the ethical guidelines of the institutional review board of all participating centers.

RESULTS

Patient Characteristics

A total of 758 patients—571 patients with Crohn disease (75.3%) and 187 patients with ulcerative colitis (24.7%)—were included. Treatment with infliximab was started after a median disease duration of 4.5 years (IQR, 1.1-12.9 years), and patients were switched to CT-P13 after a median of 4.7 years (IQR, 2.6-7.1 years). Patient and disease characteristics at baseline are depicted in Table 1. Seventy-five (9.9%) patients were reverse-switched to originator infliximab. Compared to patients maintained on CT-P13, reverse-switched patients were more often female (70.7% vs 52.0%, respectively; $P = 0.002$). The proportion of reverse-switched patients varied considerably between hospitals (range, 2.5%-29.6%; $P < 0.001$).

Reverse Switching

A total of 110 reasons for reverse switching were documented in 75 patients. Gastrointestinal symptoms (25.5%) and der-

matological adverse effects (21.8%) were the most commonly reported. Nine patients (12.0%) experienced loss of response. Overall, 73.3% of patients reported improvement or resolution of symptoms after reverse switching to originator infliximab. Psychological adverse effects and infections were found to improve in less than 50% of patients (Table 2). Seven of the 9 patients with a confirmed loss of response regained clinical response after reverse switching, which was biochemically proven in 3 patients. All 7 of these patients continued infliximab therapy until the end of follow-up. Notably, in 1 patient a partial decrease in fecal calprotectin levels was already observed before reverse switching. In addition, in 1 patient a dose intensification was first tried to no avail in the 4 months before the reverse switch. In another patient, a simultaneous reverse switch and dose intensification did not lead to a response. No other patient had a change in infliximab dosing regimen.

Reverse switching was performed after a median of 133 days (IQR, 88-242 days) after the first CT-P13 infusion. Thus, the majority of patients switched back to originator infliximab after 1 to 4 CT-P13 infusions (Fig. 1).

Clinical Outcomes and Drug Sustainability

During a median follow-up time of 1.50 years (IQR, 1.39-1.98 years), 93 out of the 683 patients (13.6%) who were maintained on CT-P13 discontinued infliximab therapy after a median of 11.0 months (IQR, 5.7-16.8 months). Total follow-up of patients maintained on CT-P13 was 1166 patient-years. During a median follow-up time of 1.51 years (IQR, 1.39-2.16 years) 12 patients who were

Table 1. Patients' Demographic and Disease Characteristics

Variables	Maintained on CT-P13	Reverse Switched	*P*
	n = 683	n = 75	
Age at diagnosis (y), median (IQR); missing: 3	24.4 (18.4-35.1)	25.3 (19.8-34.0)	0.46
Age at start of infliximab (y), median (IQR)	34.5 (24.3-48.0)	35.8 (27.0-50.3)	0.41
Time from diagnosis until start of infliximab (y), median (IQR)	4.3 (1.1-12.8)	6.5 (1.0-13.1)	0.56
Years on originator infliximab, median [IQR]	4.8 (2.6-7.2)	4.0 (2.6-6.4)	0.28
Female sex, n (%)	355 (52.0)	53 (70.7)	0.002
Current smoker	147 (24.8)	19 (27.9)	0.57
Crohn disease, n (%)	516 (75.5)	55 (73.3)	0.67
Montreal A (age, y), n (%)			
A1, <16	115 (22.4)	9 (16.4)	0.54
A2, 16-40	323 (63.0)	36 (65.5)	—
A3, >41	75 (14.6)	10 (18.2)	—
Montreal L (location), n (%)			
L1, ileal	126 (24.4)	8 (14.5)	0.35
L2, colonic	129 (25.0)	17 (30.9)	—
L3, ileocolonic	258 (50.0)	30 (54.5)	—
L4, upper GI	3 (0.6)	0 (0.0)	—
Montreal B (behavior), n (%)			
B1, pure inflammatory	291 (57.1)	29 (53.7)	0.58
B2, stricturing	117 (22.9)	11 (20.4)	—
B3, penetrating	102 (20.0)	14 (25.9)	—
Perianal disease	185 (35.9)	17 (30.9)	0.47
Ulcerative colitis, n (%)	167 (24.5)	20 (26.7)	0.67
E1, proctitis	20 (12.0)	0 (0.0)	0.14
E2, left-sided colitis	46 (27.7)	9 (45.0)	—
E3, pancolitis	100 (60.2)	11 (55.0)	—
Hospital, n (%)			
Center 1	87 (85.3)	15 (14.7)	<0.001
Center 2	94 (87.9)	13 (12.1)	—
Center 3	117 (94.4)	7 (5.6)	—
Center 4	79 (97.5)	2 (2.5)	—
Center 5	28 (90.3)	3 (9.7)	—
Center 6	19 (70.4)	8 [29.6]	—
Center 7	94 (81.7)	21 (17.9)	—
Center 8	35 (97.2)	1 (2.8)	—
Center 9	130 (96.3)	5 (3.7)	—

Female sex and hospitals showed statistically significant differences between patients maintained on CT-P13 and patients who were reverse-switched.

Table 2. Reported Reasons for Reverse Switching and Reversibility

Reasons for Reverse Switching	n (%)*	Reversible After Reverse Switch (%)†
Total of reported reasons in 75 patients	110	82 (74.5)
Gastrointestinal symptoms	28 (25.5)	23 (82.1)
Dermatological symptoms	24 (21.8)	16 (66.7)
Neurological symptoms	13 (11.8)	11 (84.6)
Rheumatological symptoms	12 (10.9)	8 (66.7)
Fatigue	10 (8.2)	9 (90.0)
Loss of response	9 (8.2)	7 (77.8)
Allergic reactions	6 (5.5)	5 (83.3)
Infection	5 (4.5)	2 (40.0)
Psychological symptoms	3 (2.7)	1 (33.3)

*Percentage of total amount of reported reasons.
†Percentage of reasons that were reversible.

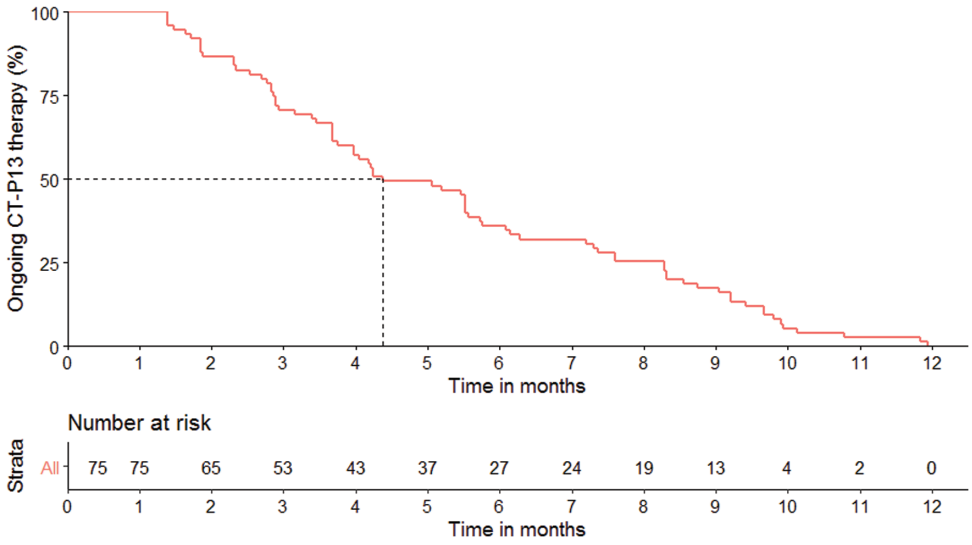

Figure 1. Survival curve of time until reverse switching within 52 weeks.

reverse-switched (16.0%) discontinued infliximab treatment after a median of 18.3 months (IQR, 12.5-20.9 months). Total follow-up time of patient who were reverse-switched was 127 patient-years. The reasons for infliximab discontinuation were not statistically different between patients who were reverse-switched and those maintained on CT-P13 (Table 3).

Graphically, there was no difference in infliximab persistence between patients who were maintained on CT-P13 and those who were reverse-switched (Fig. 2). Univariable Cox proportional hazard modeling identified female sex (HR, 1.87; 95% CI, 1.14-3.07), time on originator infliximab (HR, 0.65; 95% CI, 0.54-0.78), and reverse switching (originator infliximab/CT-P13 use as time-varying covariate; HR, 1.96; 95% CI, 1.02-3.78) to be associated with infliximab discontinuation. In subsequent multivariate Cox proportional hazard modeling, only female sex (HR, 2.01; 95% CI, 1.31-3.10), higher age at switch (HR, 2.69; 95% CI, 1.40-5.16), and time on originator infliximab (HR, 0.61; 95% CI, 0.54-0.68) remained as predictors for infliximab (dis)continuation (Table 4).

Pharmacokinetics and Immunogenicity

Infliximab trough levels before and during the initial switch and after the reverse switch were available in 48, 38, and 29 patients, respectively. In 15 patients, infliximab trough levels were available at all 3 timepoints. Within these 15 patients, the median infliximab trough levels before and during switching to CT-P13 were 5.0 mg/L (IQR, 3.7-6.8 mg/L) and 4.6 mg/L (IQR, 3.5-5.9, mg/L), respectively, and 5.8 mg/L (IQR, 4.6-7.5 mg/L) after switching back to originator infliximab (P = 0.08). Additional pairwise comparison showed that infliximab trough levels after switching back to originator infliximab were significantly higher than infliximab trough levels during CT-P13 use (P = 0.01), even after correcting for multiple comparisons (Fig. 3A). Subsequent analyses of all patients with infliximab trough levels measured before switching to CT-P13 and during CT-P13 use (n = 32), during CT-P13 use and after reverse switching (n = 18), and before switching to CT-P13 and after reverse switching (n = 23), yielded the same results (Figs. 3B-D).

However, in 4 patients the dose was increased before originator infliximab trough level measurement after reverse

Table 3. Infliximab Discontinuation Reasons

Infliximab Discontinuation	Maintained on CT-P13	Reverse-Switched	*P*
	n = 683	n = 75	
Infliximab discontinuation, n (%)	93 (13.6)	12 (16.0)	0.57
Secondary loss of response, n (%)	37 (39.8)	6 (50.0)	0.33
Adverse effects, n (%)	17 (18.3)	3 (25.0)	—
Miscellaneous, n (%)	8 (8.6)	2 (16.7)	—
Clinical remission, n (%)	31 (33.3)	1 (8.3)	—

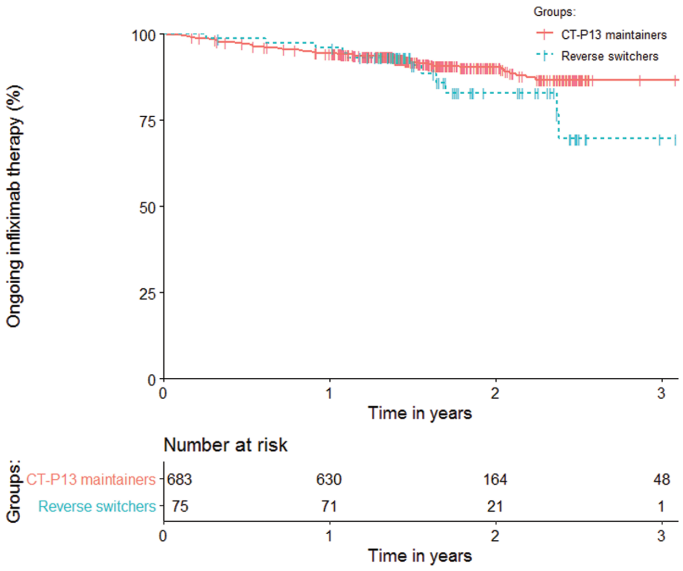

Figure 2. Kaplan-Meier survival curve depicting infliximab survival of patients who were reverse-switched and those maintained on CT-P13.

switching. After excluding these patients from the analyses, no significance remained with respect to the differences between trough levels beforeor during CT-P13 and after reverse switching.

Antidrug antibodies were not present in patients whose infliximab trough levels were measured before switching to CT-P13. No patients developed antidrug antibodies after switching to CT-P13 or after reverse switching to originator infliximab subsequently. Notably, antidrug antibodies were only measured if trough levels were <1.0 mg/L.

Discussion

In this large retrospective cohort study, we aimed to identify the prevalence of, the reasons for, and the effectiveness of reverse switching to originator infliximab in patients who were initially switched to CT-P13. Overall, reverse switching occurred in 75 of the 758 patients in the study (9.9%; range, 2.5%-29.6%), and patients who were reverse-switched were more often female. Patients were most commonly switched because of gastrointestinal symptoms or dermatological adverse effects. Reverse switching was beneficial in 73.3% of patients. Drug persistence was equal between patients maintained on CT-P13 and patients who were reverse-switched in multivariable analyses. No clinically relevant differences were seen between the pharmacokinetics of CT-P13 and originator infliximab.

Three studies have reported on reverse switching to originator infliximab after an initial switch from originator infliximab to a biosimilar in patients with IBD.[7,14,18] Our average reverse-switching rate within 52 weeks (9.9%) was slightly lower than the reported reverse-switching rates of 12.9% and 16.5% within 52 weeks.[7,14] In all 3 studies, the clinical motivations for reverse switching were predominantly a perceived loss of response or adverse effects. The clinical effectiveness of these reverse switches was not elaborated upon except in 1 study, in which all patients who were reverse-switched were successfully treated with at least 2 additional infusions of originator infliximab. The authors attributed the reverse switches to a nocebo effect, defined as a biochemically or pharmacologically unexplainable unfavorable outcome, after a switch from originator to biosimilar infliximab, which resolved after reinitiating the originator.[14]

In our study, gastrointestinal symptoms and dermatological adverse effects were found to be the most prevalent reasons for reverse switching. After reverse switching, most patients reported improvement or resolution of symptoms in nearly all categories. We postulate that most of the symptoms resulted from a nocebo effect, which was defined as the development or occurrence of events or manifestations of whatever nature which occur following switch of a drug to a biosimilar disappear when switched back to the originator.[14,15] In addition, incorrect causal attribution may also have played a role, especially in patients in whom reverse switching was

Table 4. Predictors of Infliximab Persistence After Switching From Originator Infliximab to CT-P13

Variable	Univariable	Multivariable
	HR (95% CI)	HR (95% CI)
Sex		
Male	Reference	
Female	1.87 (1.14-3.07)	2.01 (1.31-3.10)
IBD type		
Crohn disease	Reference	
Ulcerative colitis	0.99 (0.99-1.00)	0.94 (0.83-1.06)
Duration of disease	1.00 (0.98-1.02)	0.99 (0.98-1.01)
Smoking		
Nonsmoker	Reference	
Current smoker	1.05 (0.80-1.38)	0.99 (0.95-1.04)
Years of originator IFX use	0.65 (0.54-0.78)	0.61 (0.54-0.68)
Age at switch	1.78 (0.94-3.35)	2.69 (1.40-5.16)
Switching back to originator	1.96 (1.02-3.78)	1.76 (0.87-3.56)

Variables with a 95% confidence interval that did not cross or did not include 1.0 in uni- or multivariable analysis were female sex, years of originator IFX use, and age at switch.
IFX indicates infliximab.

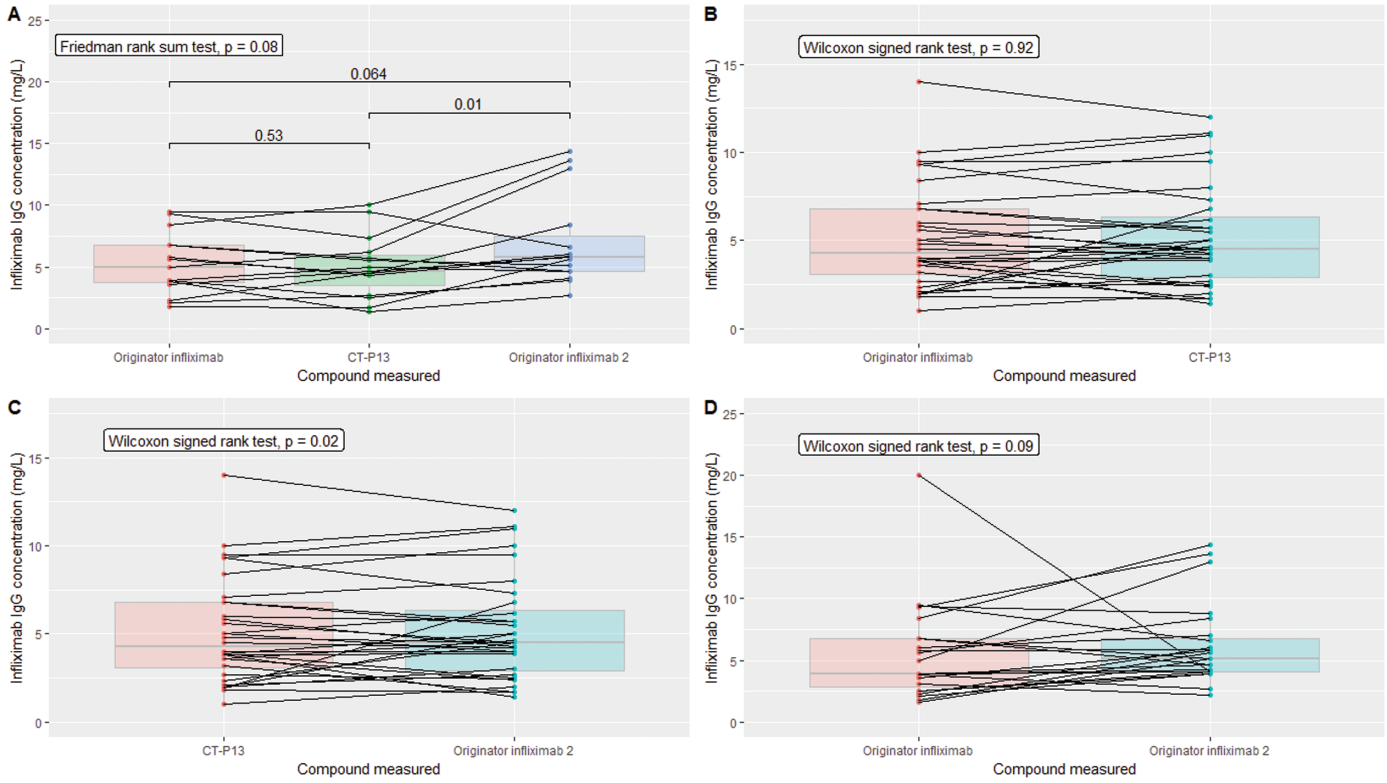

Figure 3. Infliximab trough levels of patients (A) before the initial switch, during the switch, and after reverse switching (n = 15); (B) before the initial switch and during the switch (n = 32); (C) during the switch and after reverse switching (n = 36); and (D) beforethe initial switch and after reverse switching (n = 23).

not beneficial. Incorrect causal attribution is the false attribution of symptoms to—in this case—the switch from originator infliximab to CT-P13. Note that physicians may also be subject to this phenomenon.

The nocebo effect is the antonym of the placebo effect and results from a patient's negative expectations. The generally high discontinuation rates after a switch to a biosimilar in both clinical trials and real-world evidence studies in both IBD and rheumatological diseases have recently been ascribed to this phenomenon.[15] Several factors may contribute to the nocebo effect such as prior conditioning, expectations, psychological characteristics, and situational influences.[19]

According to a survey looking into patient perspectives on biosimilar drugs in IBD, the majority of patients have doubts and concerns about the safety and effectiveness of these drugs.[20] This hesitation may first contribute to less-favorable treatment outcomes because patients' expectations before starting treatment influence treatment outcomes.[21] In addition, negative expectations may lead to negative symptoms and thus the nocebo effect.[22]

The communication between a patient and physician can set a patient's treatment expectations and thus influence the nocebo effect both negatively and positively.[23] In addition, providing patients with tailored information and educational practices surrounding a switch may counter the nocebo effect. This possibility was recently indicated in a cohort of patients switching from originator etanercept to its biosimilar, SB4. The authors had previously observed a far higher than expected discontinuation rate in a cohort switching from originator infliximab to CT-P13. They implemented a structured communication strategy in the cohort switching to SB4, after which they observed only slightly lower persistence rates compared to a historical cohort.[24,25]

The variation in outcome attributed to information and education may also have contributed to the variable percentage of patients who were switched from the biosimilar back to the originator, as observed in the various hospitals contributing to this study. In addition, no hospital had a prespecified policy on how to manage patients experiencing negative outcomes after the initial switch. Thus, it is likely that a physician's willingness to reverse-switch also contributed to this variation.

Although the nocebo effect seemed to play a role in the majority of described patients, objectified adverse effects such as new or worsening skin reactions and confirmed loss of response were encountered as well. Why most of these patients benefited from reverse switching is hard to understand, especially because the blockade of tumor necrosis factor is the mechanism considered to induce remission and is also thought to be the main immunological pathway involved in the pathogenesis of infliximab-related skin reactions.[26,27] However, although biosimilars and originators have highly similar pharmacodynamic properties, several differences do exist: notably, the glycosylation profile, which can impact the pharmacokinetics and pharmacodynamics of monoclonal antibodies. For example, compared to originator infliximab, lower binding of CT-P13 to FcγRIIIa, which is involved in antibody-dependent cell-mediated cytotoxicity, has been observed. However, the clinical relevance of these observations is unclear.[28-30]

In addition, loss of response may also be secondary to low infliximab trough levels.[31] Of the patients with measured infliximab trough levels, >70% were above the Dutch recommended threshold value of 3 mg/L.[32] One patient who was reverse-switched with established loss of response had a subtherapeutic drug level of 0.8 mg/L. This patient did not regain response after reverse switching and receiving a double dose of originator infliximab. However, no previous trough levels were available for this patient. Thus, overall data on infliximab trough levels were too scarce to establish a causal relationship with loss of response.

In our cohort, most patients who were reverse-switched were female. Female sex has been shown to be a risk factor for developing adverse reactions to drugs, in general thus possibly contributing to the female predominance among patients who were reverse-switched.[33,34] Furthermore, the nocebo effect is reported to be stronger and more frequent in women than in men.[19,35] In addition, we found that female sex was a predictor for infliximab drug discontinuation, corroborating recent results.[36]

Our results regarding the effectiveness of CT-P13 are comparable or better than reported from real-world observational cohorts and clinical trials.[6-8,10-12] Not considering the patients who reverse-switched, 13.6% of patients discontinued CT-P13 treatment during a median follow-up time of 1.50 years (IQR, 1.39-1.98 years). This result is on the lower spectrum of the reported discontinuation rates of 7.5% to 29% within 1 year.[7,9] In addition, we found that longer originator infliximab use was associated with a decreased risk of infliximab discontinuation, which we attributed to the healthy survivor bias. An increased risk of infliximab discontinuation was found for patients with a higher age at the time of switching to CT-P13, supporting recent results.[37]

Although this study was conducted in a relatively small group, we did not find any clinically relevant differences in pharmacokinetics between CT-P13 and originator infliximab, corroborating findings from larger cohorts and a recent randomized controlled noninferiority trial.[10,13] In the open-label SECURE trial, serum concentrations of CT-P13 did not differ from originator infliximab levels at 16 weeks after switching to CT-P13. Furthermore, no differences in immunogenicity were observed between baseline and follow-up.[38] When patients were switched from CT-P13 to originator infliximab, differences in neither pharmacokinetics nor immunogenicity were seen.[16] These observations may be explained by their highly similar immunogenicity, suggesting shared immunodominant epitopes.[39]

Note that our results are only applicable for switching between originator infliximab and CT-P13 and vice versa. It remains to be seen whether this is also the case for the infliximab biosimilar SB2 or for cross-switching between various biosimilars. Such a finding may be feasible because immunogenicity data in IBD suggests that SB2 has the same immunodominant epitopes as originator infliximab and CT-P13.[40]

The strengths of our study include the relatively large multicenter cohort of both tertiary referral centers and general hospitals. Therefore, our population represents the average patient with IBD, making our results more generalizable. In addition to data on the prevalence of reverse switching, we were able to report on the reasons for and clinical effectiveness of reverse switching. Our data may support clinical decision-making in countries where switching to biosimilars is now getting a firm foothold. In addition, our results may give clinicians some guidance on how to cope with the arrival of newer biosimilars, most recently adalimumab biosimilars. Our data also highlight the importance of raising the awareness of a possible nocebo effect in future trials or prospective cohorts investigating switching to biosimilars.

Several limitations to our study have to be addressed. Most are inherent to the retrospective study design, such as missing data. For example, fecal calprotectin measurements were so infrequently performed that we could only use these data to define loss of response. In addition, a detailed report of the reasons for reverse switching could not be retrieved for the most part because of the absence of predefined documentation guidelines and parameters. Furthermore, misclassification bias of symptoms for reverse switching to originator infliximab, discontinuation, and reversibility of symptoms are unavoidable because of the lack of standardized criteria at the

time of the event. In addition, because of their relatively small size, meaningful subgroup analyses were not feasible. Thus, differences between ulcerative colitis and Crohn disease with respect to loss of response could not be determined. Finally, immunogenicity could not be assessed because only reactive therapeutic drug monitoring was performed and infliximab-neutralizing antibodies were only measured if trough levels were <1.0 mg/L.

Conclusions

We report that reverse switching to originator infliximab occurred in 9.9% of patients after a switch to CT-P13. In patients experiencing negative outcomes after a switch to CT-P13, reverse switching to originator infliximab is a reasonable option. In this study, reverse switching was beneficial in 73.3% of patients and did not lead to differences in drug survival between patients remaining on CT-P13 or in whom originator infliximab was reintroduced. Thus, reverse switching may be considered if negative outcomes of an initial switch to CT-P13 do occur.

Author contributions

HF: guarantor of the article. SM, JS, and HF: conception and design. SM, JS, AvB, GD, FH, AM-J, LG, ML, NM, AT: generation of data. SM, JS, and LS: acquisition of data. SM, JS, BO, and HF: analysis and interpretation of data. JS, BO, and HF: drafting of manuscript. All authors: critical revision of manuscript for important intellectual content, approval of final version of manuscript and authorship list.

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Conflicts of interest

AvB has been a consultant for medical issues or provided paid lectures for AbbVie, Biogen, Ferring, Janssen-Cilag, MSD, Pfizer, Samsung, Takeda, TEVA, and Tramedico. GD has received unrestricted research grants from AbbVie and Takeda; has served as a member of the advisory board for Mundipharma and Pharmacosmos; and has received speaker fees from Takeda, Pfizer, and Janssen. FH has served on advisory boards or as a speaker for AbbVie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk; has served as a consultant for Celgene; and has received unrestricted research grants from Dr Falk, Janssen-Cilag, and AbbVie. AM-J has served as a speaker for Janssen and Takeda, has served as a consultant for Takeda, and has received a research grant from Takeda. BO reports grants from MSD, AbbVie, Takeda, Cablon, Ferring, Dr Falk, and Pfizer. HF has done consultation for AbbVie BV, Janssen BV, Ferring BV, and Takeda BV. The remaining authors declare no conflicts of interest.

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