Evaluating Efficacy, Safety, and Pharmacokinetics After Switching From Infliximab Originator to Biosimilar CT-P13: Experience From a Large Tertiary Referral Center

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Background: The use of infliximab biosimilar CT-P13 has increased in patients with inflammatory bowel disease. Nevertheless, doubts about switching from infliximab originator to biosimilar still exist among patients and health care professionals.

Methods: Our tertiary referral center underwent a mandatory switch from infliximab originator to CT-P13 in 2017. We investigated pharmacokinetics, efficacy, and safety of this switch. The primary endpoint was infliximab discontinuation within 6 months of switching. Secondary endpoints included loss of clinical remission, need for treatment optimization, adverse events, evolution of patient-reported outcome, C-reactive protein, infliximab trough levels, and antidrug-antibodies.

Results: A total of 361 patients (54.0% male, 70.0% Crohn's disease, 55.6% in clinical remission) were enrolled. Infliximab discontinuation within 6 months was observed in 4%. Loss of clinical remission, adverse events, and antidrug-antibodies were identified in only 2.0%, 2.2%, and 1.1% of patients, respectively. C-reactive protein concentrations and infliximab trough levels remained stable. Independent factors associated with remission at 6 months were lower PRO2 at switch (HR 6.024; 95% CI, 4.878–8.000; $P < 0.0001$) and higher hemoglobin levels (HR 1.383; 95% CI, 1.044–2.299; $P = 0.018$).

Conclusions: Switching from infliximab originator to CT-P13 was not associated with an increased risk of treatment discontinuation, loss of clinical remission, or adverse events. No significant changes in infliximab trough levels or immunogenicity could be identified.

Key Words: infliximab, biosimilar, switching, CT-P13, trough levels

INTRODUCTION

Infliximab, a chimeric IgG1 monoclonal antibody targeting tumor necrosis factor alpha (TNF), has significantly improved patient outcomes in immune-mediated inflammatory disorders, including inflammatory bowel disease (IBD). With anti-TNF agents, one could achieve not only clinical remission but also mucosal healing, which is linked to lower need for hospitalization and surgery and subsequent better quality of life. Perhaps fueled

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Abbreviations: ADAs, antidrug antibodies; ANAs, antinuclear antibodies; CD, Crohn's disease; CS, corticosteroids; ELISA, enzyme linked immunosorbent assay; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease type unclassified; IFX, Infliximab; IM, immune modulator; TLs, trough levels; TNF, Tumor necrosis factor; UC, ulcerative colitis.

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by its success, health care expenditures have now shifted from surgery and hospitalization to the use of biologicals.[1,2]

After patent expiration of infliximab (IFX) originator Remicade (Janssen Biotech, Horsham, Pennsylvania, USA), 2 CT-P13 IFX biosimilars, Remsima (Mundipharma International Limited, Cambridge, UK) and Inflectra (Hospira, Lake Forest, Illinois, USA), have been introduced after approval by the European Medicines Agency in 2013. Approval by the US Food and Drug Administration followed in 2016. Introduction of these biosimilars into the European market has already aided in reducing health care costs, achieving price reduction up to 39% per treatment day in certain European countries.[3] An additional decline in costs is to be expected as more patients with IBD will be switched from originator to CT-P13 and other biosimilars enter the market. Despite approval for the 6 known indications of infliximab, safety and efficacy data concerning switching to CT-P13 among IBD patients specifically are still lacking. The only randomized controlled data leading to the approval of CT-P13 originated from studies performed in patients with ankylosing spondylitis[4] and rheumatoid arthritis.[5]

In June 2017, several years after the approval by the European Medicines Agency, a large randomized controlled noninferiority trial was published (NORSWITCH),[6] showing that switching to CT-P13 was noninferior to continued treatment with IFX originator. Although this study contained 248 IBD patients (51%), it was not powered to show noninferiority among patients with Crohn's disease (CD) and ulcerative colitis (UC). Efficacy and safety in switching from originator to CT-P13 in IBD patients, therefore, remains to be proven. Furthermore, most studies do not contain a control population,[7–14] emphasized on trough levels (TLs),[15] lacked measurements of TLs or antidrug-antibodies (ADAs)[11, 16, 17] or were limited by size.[8, 10, 14, 18, 19] The scarcity of large studies in patients with IBD specifically could play a role in the persisting uncertainty among patients and health care professionals concerning the switch to CT-P13 or other biosimilars.

The aim of this study was to investigate the pharmacokinetics, efficacy, and safety of a mandatory switch from IFX originator to CT-P13 in patients with CD and UC in a real-life setting.

MATERIALS AND METHODS

Patient Population

In the IBD unit of our tertiary referral center, CT-P13 was introduced in a 2-step procedure. The infliximab biosimilar CT-P13 was first prescribed in all IFX-naïve patients initiating IFX for IBD from November 2015 onward. At that stage, all IFX-exposed patients continued the IFX originator. As for the originator, CT-P13 was started at a dose of 5 mg/kg at weeks 0, 2, and 6 in most cases, with maintenance treatment every 8 weeks thereafter. In March 2017, the hospital imposed a mandatory switch of all patients receiving maintenance treatment with IFX originator to CT-P13. For the main analysis, all IBD patients who were switched collectively from the infliximab originator to CT-P13 in March 2017 were included. Initially, a control group was also included, which consisted of IFX-naïve patients, initiating CT-P13 from November 2015 onward. However, due to intrinsic limitations of this group, the controlled data were only included as a supplementary analysis.

Patients with an ileostomy or ileal pouch-anal anastomosis were excluded. The total duration of follow-up was 6 months. At every infusion, patients systematically received clinical and biochemical evaluations, of which the time interval depended on the individual infusion interval. As part of daily clinical practice, IFX interval could be adapted according to TLs and/or clinical evolution.

Variables of Interest

Clinical and demographical data were collected from patients' electronic medical records. The following baseline variables were collected: sex, age at diagnosis, disease location and behavior according to the Montreal classification,[20] extra-intestinal manifestations, previous need for surgery, smoking status, comorbidities, initial indication for IFX, and disease duration. Concomitant use of disease-modifying drugs was also recorded, being defined as synchronously adjunctive therapies such as corticosteroids and azathioprine at inclusion. During follow-up, the subsequent adverse events were registered: infections necessitating hospitalization, development of skin problems, arthralgia or malignancies, infusion reactions, development of antinuclear antibodies (ANAs), and occurrence of death.

Patient-reported outcome (PRO2), C-reactive protein (CRP), IFX trough levels, and ADAs were measured at the first infusion of CT-P13 after March 2017 (T0, baseline, moment of switch), the next infusion of CT-P13 (T1), and 6 months later (T2). This was prospectively performed after the mandatory switch was announced by the hospital. Laboratory tests, including hemoglobin, CRP, and serum albumin, were extracted from the medical records for T0, T1, and T2. Serum samples were collected right before each IFX infusion and stored in our biobank, of which samples of T0, T1, and T2 were thawed to measure IFX TLs by infliximab ELISA (apDia, Turnhout, Belgium). Antidrug-antibodies were evaluated not only through a drug-sensitive assay anti-IFX ELISA (apDia, Turnhout, Belgium) in case of undetectable TLs (<0.5 µg/mL) but also by a drug-tolerant assay (cut-off TLs < 3 µg/mL). Antidrug-antibodies were considered positive when detected on at least 1 occasion.

Endpoints

The primary endpoint was IFX discontinuation for any reason within 6 months after the index infusion (first IFX infusion after March 2017). Secondary endpoints included loss of clinical remission, need for treatment optimization,

development of adverse events, development of new ADAs, and evolution of PRO2, CRP, and IFX TLs. Clinical remission was based on PRO2 and defined as a rectal bleeding score of 0 and a stool frequency ≤1 for UC[21] or an abdominal pain score ≤1 and liquid to very soft stool frequency ≤1.5 for CD.[22] The term "loss of clinical remission" was used to describe patients who were in clinical remission at T0 but did not meet criteria for clinical remission at T1 or T2. Treatment optimization was defined as the need for changes in IFX dosage or introduction of additional disease-modifying drugs.

Statistical Analyses

The IBM SPSS Statistics 25.0 software package (Armonk, NY, USA) was used for statistical analyses. For discrete data, proportions and percentages were reported, whereas for continuous data, medians with interquartile ranges (IQRs) were presented. To compare the evolution of TLs, PRO2, and CRP between time points, paired analyses were performed by using the Wilcoxon signed-rank test. We used χ^2 for categorical data and Mann-Whitney *U* test for continuous data in our univariate analysis. Multivariate analysis was performed by binary logistic regression. A 2-tailed *P* value <0.05 was regarded as statistically significant.

ETHICAL CONSIDERATIONS

The study was approved by the Institutional Review Board of the University Hospitals Leuven (B322201213950/S53684), and informed consent was obtained from all participants.

RESULTS

Patient Characteristics

A total of 361 patients were enrolled, 54.0% of which were male, with a median age of 25 years at diagnosis. The majority of patients (70%) had CD, and 62% of patients were in clinical remission at T0. Furthermore, median disease duration was 7.0 years, median duration of IFX treatment was 6.0 years, and adjunctive immunomodulatory therapy was given in 6% of patients at the moment of switch. At the switch, median CRP concentrations were low (1.5 mg/L). Demographical data and disease characteristics are outlined in Table 1.

TABLE 1. Patient Characteristics

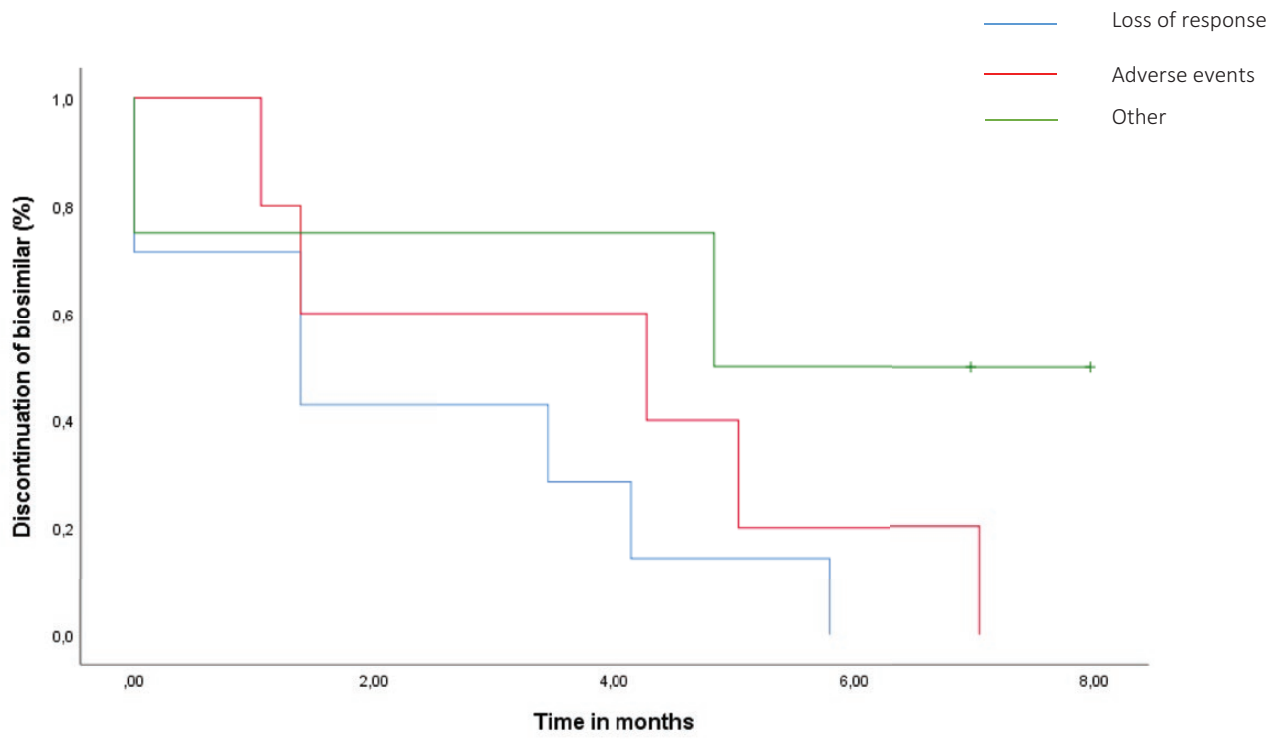
Demographics	(Total = 361)
Male (%)	196/361 (54%)
Diagnosis (% CD)	251/361 (70%)
Median age at initial diagnosis (IQR, years)	25 (19–34)
Clinical remission (%)	223/361 (62%)
Disease location (%CD):	
L1	50/251 (20%)
L2	49/251 (20%)
L3	151/251 (60%)
L4	1/251 (0.4%)
Disease behaviour (CD):	
B1	98/251 (39%)
B2	77/251 (31%)
B3	76/251 (30%)
P	19/251 (8%)
Disease extent (UC):	
E1	5/101 (5%)
E2	41/101 (41%)
E3	55/101 (54%)
Median disease duration (IQR, years)	7.0 (1–13)
Median duration of IFX therapy (IQR, years)	6.0 (3–10)
Median time between diagnosis and start IFX (IQR, years)	6.7 (1–13)
Median C-reactive protein (IQR, mg/l)	1.5 (0.7–3.6)
Median serum albumin (IQR, g/l)	43 (41–45)
Median Hemoglobin (IQR, g/dl)	13.8 (12.8–14.6)
Concomitant IM	23/361 (6%)
Concomitant CS	6/361 (2%)

Abbreviation: P: perianal disease

Efficacy

During the follow-up of 6 months, CT-P13 was discontinued in 15 patients (4%). Discontinuation was predominantly attributed to loss of clinical remission (n = 8) and development of adverse events (n = 5). After CT-P13 discontinuation, 6 patients were switched to vedolizumab, 3 patients were switched to ustekinumab, 1 patient was switched to adalimumab, and 5 patients did not continue biological therapy. Univariate analyses were performed, and the only variables that were associated with good therapeutic outcome (clinical remission based on PRO2 at T2) were a higher hemoglobin level (HR 1.383; 95% CI, 1.044 to 2.299; $P = 0.018$) and a lower PRO2 score (HR 6.024; 95% CI, 4.878 to 8.000; $P < 0.0001$) at T0 (switch from IFX originator to biosimilar). Likewise, independent factors associated with clinical remission at T2 were higher hemoglobin levels (HR 1.277; 95% CI, 1.042 to 1.565; $P = 0.018$) and lower PRO2 at switch (HR 1.165; 95% CI, 1.125 to 1.205; $P < 0.0001$). Furthermore, a time to event analysis was performed for treatment discontinuation, loss of response, and serious adverse events (Fig. 1).

Absence of treatment optimization was seen in 75% of patients, whereas 48 patients (13%) developed loss of clinical remission. Univariate analysis (Mann-Whitney *U* test) demonstrated that lower median age (39 [IQR 31 to 49] vs 44 [IQR 32 to 55], $P = 0.018$), shorter duration of IFX therapy (5 years [IQR 3 to 9] vs 7 years [IQR 4 to 10], $P = 0.012$), and higher CRP levels (2 mg/L [IQR 0.6 to 4.1] vs 1.3 mg/L [IQR 0.5 to 2.9] $P = 0.042$) were associated with absence of treatment optimization. Primary and secondary endpoints are outlined in more detail in Table 2.



Discontinuation due to loss of response	6	3	1	0	0
Discontinuation due to adverse events	4	3	1	0	0
Discontinuation due other reasons	3	3	3	2	1

FIGURE 1. Time to event analysis for drug discontinuation, loss of response, and serious adverse events.

Therapeutic Drug Monitoring

Although median TLs increased slightly at T1, median TLs did not change significantly over the duration of 6 months ($P = 0.59$) (Table 3), and CRP remained stable over time ($P = 0.39$) (Fig. 2). We also performed a time trend analysis by means of 1-way analysis of variance (ANOVA), which revealed a P value of 0.611. Therefore, it seems that trough levels at T0 cannot predict whether a patient remained in remission at T2.

New ADAs were identified in 4 patients (1.1%), which were all detected by the drug-tolerant assay and did not lead to loss of clinical remission or discontinuation of IFX. The drug sensitive assay failed to detect ADAs in 3 out of 4 patients. No infusion reactions were observed in both groups.

Safety

Adverse events occurred in 2.2% of patients, which were in most patients dermatological (2%), with a predominance of eczematous eruptions. Only 2 infections necessitating hospitalization were identified (0.6%): one patient developed a pneumonia, and the other contracted a *Campylobacter jejuni* infection. Antidrug antibody positivity was detected in 30%.

DISCUSSION

The main evidence of switching to CT-P13 mainly originates from observational studies and subsequent systematic reviews. In 2018, a large systematic review was published that included 1326 patients and evaluated the effectiveness and safety of switching to biosimilar CT-P13, confirming persistent disease control in most patients, with 86% of CD patients and 93% of UC patients maintaining disease control. However, this review was still limited by relatively low sample size of individual studies, as most included studies contained less than 100 patients.[23, 24] Only recently, a large comparative cohort study in patients with CD was published, which contained 5050 patients and compared effectiveness of CT-P13 with IFX originator.

Although CT-P13 seemed equally effective, switching was not evaluated, as all patients were IFX-naïve.[25] The paper of Ye et al, however, did evaluate switching of CT-P13 to infliximab originator and vice versa in CD patients and found CT-P13 to be noninferior to infliximab originator.[26]

We hereby present one of the largest prospective studies to date evaluating efficacy, safety, pharmacokinetics, and immunogenicity of switching from IFX originator to CT-P13.

During the 6 months of follow-up in the present study, switching from IFX originator to CT-P13 led to IFX discontinuation in 4% of all patients, which is lower than reported in previous articles, where discontinuation rates varied from 5.3%[16] to 26%.[7] Compared with earlier work, we observed similar rates of infusion reactions[8, 14] and loss of clinical remission.[8, 9, 12, 16, 18, 27] Very low rates of adverse events were seen in our population (2.7%) compared with a varying incidence of 7%–29%.[8, 14, 16, 27, 28] Furthermore, low rates of new ADAs were observed (1.1%), whereas in previous work, ADA prevalence varied between 3% and 9%.[7, 9, 14, 18, 28] Use of azathioprine or other immunomodulatory drugs is unlikely to explain this observation, as we observed a very low use in our patients (6% vs 46%–66% in other studies).[9, 12, 14, 18, 28] The low immunogenicity can probably be explained by the proactive therapeutic drug monitoring implemented in our hospital, resulting in high median TLs at the start of CT-P13 (5.5 µg/mL) compared with other articles (2.9 to 5.3 µg/mL).[7, 9, 12, 18, 28] When comparing median TLs between time points, we detected a temporary, nonsignificant elevation of median TLs (Table 3), a phenomenon which was also reported by Kolar et al.[18] Also, a significant increase in PRO2 was seen, which can possibly be explained by prolonged treatment with IFX, which is associated with an increased risk of disease flare and loss of clinical remission over time. Still, low rates of loss of clinical remission were identified.

Initially, our study was designed as a prospectively controlled study, comparing patients who were switched from the IFX originator to CT-P13 (cases) with continued treatment with CT-P13 in IFX-naïve patients (controls). During the 6 months of follow-up, switching from IFX originator to CT-P13 did not lead to an increased rate of IFX discontinuation, and no significant differences were seen in the percentage of patients developing loss of clinical remission, adverse events, and ADAs (see online supplementary materials). On the contrary, IFX discontinuation was detected more frequently in the control arm. The observation that controls discontinued IFX more frequently could partly be explained by a higher disease activity at baseline, demonstrated by a higher CRP level; although rates of clinical remission and median PRO2 were similar in cases and controls. Another possible explanation lies within the fact that cases were clearly IFX responders, whereas individual efficacy among controls still had to be proven. We also found that controls had increased use of immunomodulatory therapy and needed treatment optimization more frequently, presumably owing to the more recent diagnoses and IFX introduction among controls. As we detected significant differences between both groups at baseline, which may reflect worsened outcomes in controls, we decided to omit our control group from the final article. However, the data of our controlled analysis may yet be another comforting sign that patients who were switched to CT-P13 certainly did not have worse outcomes than patients on continued treatment.

Our study in the present form, without the control group, has several limitations that need to be addressed. First, endoscopic findings and fecal calprotectin values were not included in the end points. Though fecal calprotectin values are currently routinely

TABLE 2. Primary and Secondary Endpoints

	(Total: 361)
IFX discontinuation	15/361 (4%)
Loss of clinical remission	48/361 (13%)
Total need for treatment optimization	90/361 (25%)
Total adverse events	8/361 (2.2%)
Of which:	
Infection	2/360 (0.6%)
Dermatological AEs	6/361 (2%)
of which eczematous	2/6 (33%)
Infusion reactions	0/361 (0%)
Gastrointestinal malignancies	0/361 (0%)
Non-GI malignancies	0/361 (0%)
New ADAs	4/361 (1.1%)
Mortality during follow-up	0/361 (0%)
ANAs +	99/331 (30%)

Abbreviations: AEs, adverse events; ADAs, anti-drug antibodies; ANs, anti-nuclear antibodies

TABLE 3. Median PRO2, CRP, and TL at Different Time Points

	T0	T1	T2	P_a
Median (IQR) PRO2	2 (0–9)	2 (0–9)	2 (0–12)	<0.001
Median (IQR) CRP (mg/l)	1.4 (0.6–3.5)	1.4 (0.6–3.2)	1.4 (0.7–3.1)	0.39
Median (IQR) IFX TL (µg/ml)	5.5 (3.9–7.7)	5.7 (4.1–8.1)	5.5 (4.0–7.7)	0.59

[a]Evolution of CRP, IFX TL, PRO2 between T0 and T2 (Wilcoxon ranked sum test).

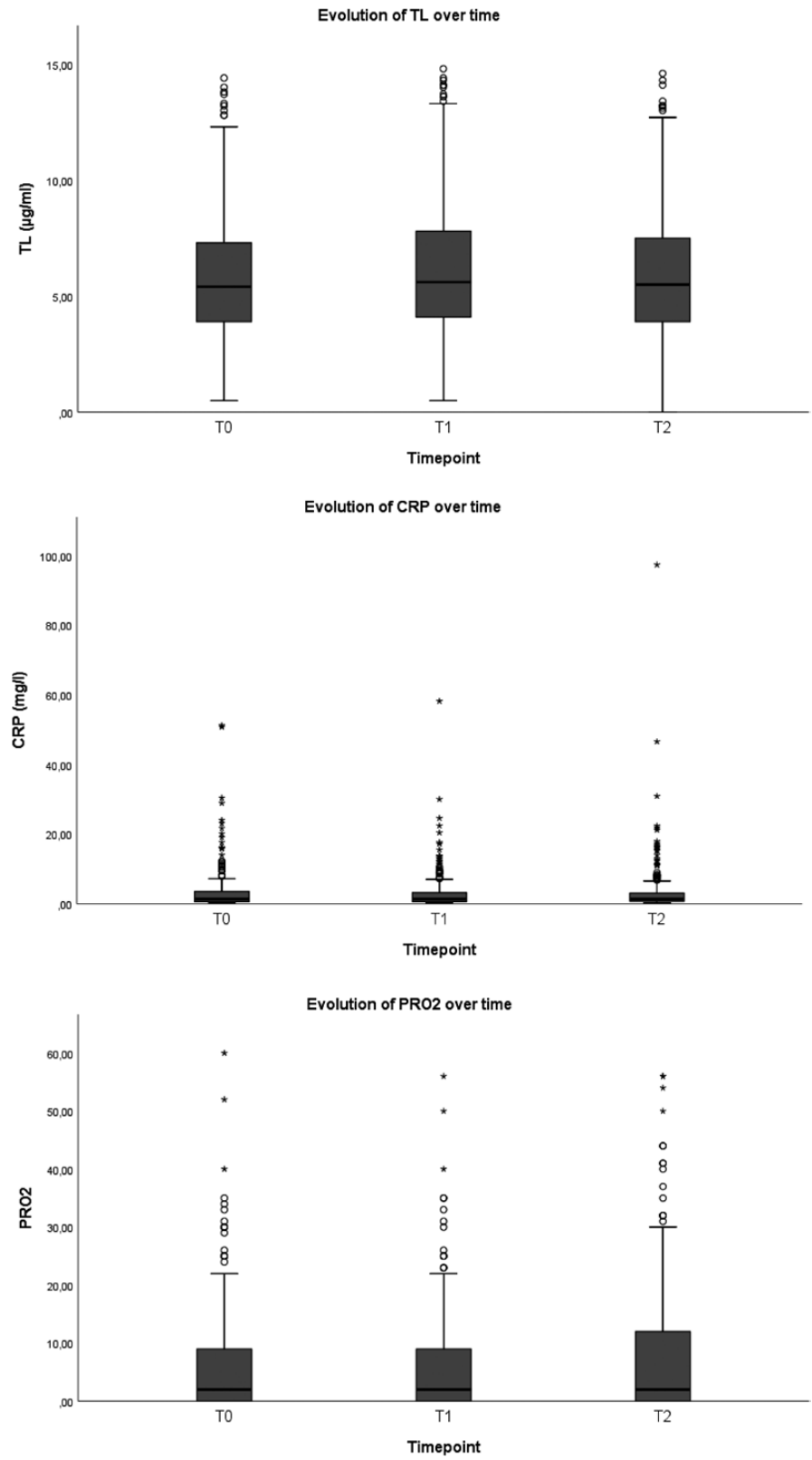


FIGURE 2. Evolution of TL, CRP, and PRO2 over time,

used for follow-up of CD, they were not systematically assessed at the beginning of the study. Furthermore, endoscopic findings were not included in the efficacy end points, as the majority of patients did not undergo their follow-up endoscopy during the specific time frame of 6 months. Although performing a colonoscopy at T0 and T2 would have been quite informative, this would have brought forth ethical and financial issues. Secondly, similar to the NORSWITCH-trial, our study was also not powered to compare outcomes between UC and CD. And finally, patients were in follow-up for the duration of 6 months, though recent data have been published with a follow-up of 1 or 2 years.[23, 29]

One of the strengths of our paper is clearly the size of our cohort, as most other studies contain 200 patients or less.[7–14] Furthermore, compared with other studies, we systematically assessed immunogenicity by serial serum samples at different time points with continuous measurements of TLs and ADAs.[11, 16, 28, 30] Lastly, in our study, clinical remission was defined by the use of PRO2, which enabled us to wield a more specific and patient-directed tool in defining loss of clinical remission—especially when comparing the use of the investigator's evaluation as a diagnostic tool[16] or relying on serum parameters and fecal calprotectin only.[9, 18]

Switching from IFX originator to CT-P13 did not lead to an increased rate of treatment discontinuation, loss of clinical remission, adverse events, or ADAs. With the increasing data of observational studies and recently published systematic reviews, switching from IFX originator to biosimilar CT-P13 seems safe and efficacious.

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