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Efficacy, pharmacokinetics and immunogenicity is not affected by switching from infliximab originator to a biosimilar in pediatric patients with inflammatory bowel disease.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Background: Rising evidence demonstrates that there are no differences in efficacy and safety between infliximab (IFX) originator and IFX biosimilar CT-P13 in the treatment of inflammatory bowel diseases (IBD). However, most data are derived from adult patients and data on pharmacokinetics are limited. The authors evaluated long-term IFX trough levels, immunogenicity and remission rates in children with IBD who switched from IFX originator to biosimilar CT-P13.

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Methods: In this single-center study, all children with Crohn's disease (CD) and ulcerative colitis (UC) receiving maintenance IFX therapy were switched from originator to biosimilar CT-P13. Demographics, disease activity indices and IFX drug levels were collected from six months before (baseline) till six months after switching to CT-P13. All data are presented as median (interquartile range).

Results: A total of 42 children (26 CD and 16 UC), with a median duration on IFX originator of 13.5 (6.8-35.5) months prior to switching to CT-P13 were included. No significant changes in IFX trough levels occurred after switching. The median baseline IFX trough level was 5.7 µg/mL (3.8-9.3) versus 6.5 µg/mL (3.9-8.6) at month six after switching (p= 0.900). Antibodies to IFX appeared in one patient after switching. The proportion of patients in clinical and/or biological remission did not significantly change after switching (all p> 0.05). No significant changes were observed in C-reactive protein, erythrocyte sedimentation rate, albumin, weight and body mass index after the switch. Safety profile was also comparable.

Conclusion: Pediatric IBD patients on IFX originator can be successfully switched during maintenance to biosimilar CT-P13 without affecting efficacy, pharmacokinetics, immunogenicity or safety.

Keywords: biosimilar, children, inflammatory bowel disease (IBD), infliximab (IFX), pharmacokinetics

Introduction

The scenery of inflammatory bowel disease (IBD) in children has drastically changed since the introduction of anti□tumor necrosis factor monoclonal antibodies such as infliximab (IFX).[1-5] However, despite the undisputed efficacy of IFX, the economic burden on healthcare systems becomes substantial due to the high costs associated with biologicals. After expiration of the patent of the IFX originator (Remicade; Janssen Biotech, Horsham,

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Pennsylvania, USA), CT-P13 was the first IFX biosimilar to be approved by the regulatory agencies, in 2013 by the European Medicine Agency (EMA) and in 2016 by the Food and Drug Administration (FDA).[6-7] Today, CT-P13 biosimilars are commercialized under different brand names, including Remsima (Celltrion, Yeonsu-gu, Incheon, Republic of Korea) and Inflectra (Hospira, Lake Forest, Illinois, USA). This, in addition, opened the market for a second IFX biosimilar SB2, also known as Flixabi (Samsung Bioepis, Yeonsu-gu, Incheon,Republic of Korea) and Renflexis (Merck, Kenilworth, New Jersey, USA). These IFX biosimilars were approved for the same indications as the originator drug, including pediatric IBD with the potential offer to reduce the financial burden and to widen the access to these drugs.[6-8]

However, the question of whether it was justified to use IFX biosimilars in IBD was raised, especially since the approval was based upon extrapolation of extensive in vitro studies[9] and only two randomized controlled clinical trials in adult non-IBD patients with ankylosing spondylitis and rheumatoid arthritis.[10-11] In response to this concern among IBD specialists, emerging post-marketing studies[12-15] and real-life data were published.[16-18] Based on these data, a recent European Crohn's and Colitis Organization (ECCO) guideline states that there are no significant differences in efficacy and safety between CT-P13 and its originator, including for patients who are IFX-naive or have been switched from the originator to CT-P13.[19] However, most of these studies were performed in adults and only two small pediatric studies have investigated the long-term follow-up of biosimilars in children.[20-21]

Hence, additional data addressing efficacy, pharmacokinetics, immunogenicity and safety of CT-P13 especially in pediatric IBD, are still desirable.[20-21] In addition, a high priority was given by the European Society for Pediatric Gastroenterology, Hepatology And Nutrition (ESPGHAN) Pediatric IBD Porto Group, to perform these pediatric trials to support the use of biosimilars in children.[22] Therefore, the aim of this study was to evaluate the long-term

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changes in IFX trough levels, immunogenicity and remission rates after switching from the IFX originator to the biosimilar CT-P13 in pediatric IBD patients during maintenance therapy.

Methods

PATIENTS AND STUDY DESIGN

A prospective, observational study was conducted in all children who initiated IFX therapy at our tertiary referral center for the treatment of active Crohn's disease (CD) or ulcerative colitis (UC). Only patients who received maintenance IFX therapy between July 2017 and January 2018 could be included in the study. Eligible subjects were patients who had been receiving the originator Remicade for at least four months (in order to receive at least one maintenance infusion of the IFX originator before switch). In our center, as of January 2018 all pediatric patients treated with Remicade were mandatorily switched to the IFX biosimilar CT-P13 (Inflectra). The switch was imposed by the hospital for all patients regardless of the indication. All of the patients and patients' parents were informed in written and oral form before the switch to IFX biosimilar CT-P13 (Inflectra). Patients were followed for six months after switching from the originator to CT-P13. At the point of switching, CT-P13 was administered as per the previous maintenance dose and dosing interval of Remicade. However, dose adaptations of CT-P13 were permitted based on the previous IFX trough levels. All children received standard pro-active therapeutic drug monitoring during maintenance treatment, even when they were asymptomatic. Using a serum sample collected right before each IFX infusion, the drug concentration was measured, and dose adaptations were made aiming to target a therapeutic window between 3-7 µg/mL (conform adult studies[23]). The Ethical Committee of our university hospital approved the study (Approval No: S59870, April 10, 2017).

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Patients' characteristics were retrieved from electronic medical records. These included demographic data (age at diagnosis, sex and IBD type), disease classification (according to the Paris classification at diagnosis), details on IFX therapy (disease duration prior to start IFX therapy, duration on Remicade treatment at time of switch and dosing schedule throughout the total follow-up period), concomitant treatment at start and during IFX therapy (mesalazine, steroids, thiopurines and/or methotrexate) and co-morbidity data at last follow-up.

Given that the time point of switching was announced to all patients in advance, as from six months prior to switching to the biosimilar CT-P13, clinical and laboratory data were collected at the time of each patient visit in order to follow the evolution of these data throughout the total study period of one year (six months prior to until six months after switching to CT-P13). Disease activity was determined and mentioned in the medical records using PCDAI (Pediatric Crohn's Disease Activity Index) for CD[24] and the PUCAI (Pediatric Ulcerative Colitis Activity Index) for UC[25]. IFX doses and intervals were recorded and expressed as a standardized IFX dose per 8-week interval. Patients' biometrics (body weight, height and body mass index (BMI)) were documented and expressed by standard references using age and sex specific references from the Belgium, Flanders 2004 growth charts.[26] All patients were asked to report any infection or other health problems emerging between administrations of consecutive doses of IFX.

Standard laboratory tests were performed prior to each IFX infusion: hemoglobin, platelets, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin and serum IFX trough levels. These data were stored in the electronic medical records. The levels were determined by Ridascreen IFX monitoring enzyme-linked immunosorbent assay (R-Biopharm, Darmstadt, Germany) which has a lower limit of quantification of 0.3 µg/ml and an upper limit of quantification of 12 µg/ml using a 1/100 serum dilution. This Ridascreen

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IFX assay is coated with tumor necrosis factor on the plate and the monoclonal antibody to IFX (MA-IFX) 6B7-horseradish peroxidase conjugate is used to identify bound IFX. MA-IFX6B7 is a non-neutralizing antibody directed against the Fab region of IFX. The Ridascreen IFX assay equally well quantifies originator and CT-P13 IFX.[27] Antibodies to IFX (ATI) were determined by an in house developed drug sensitive bridging assay if the IFX trough level was undetectable.[28]

ENDPOINTS

The primary aim of this study was to evaluate whether there was a significant difference between IFX trough levels and/or ATIs after switching to the biosimilar CT-P13 during a total period of one year. The secondary aim was to evaluate whether the proportion of patients in clinical and/or biological remission was similar before and after switching to CT-P13. Clinical remission was defined as a PCDAI/PUCAI less than 10.[29-30] Biological remission was defined as CRP ≤5 mg/L in combination with an ESR ≤20 mm/h, in patients with elevated inflammatory markers at start of IFX originator therapy.[14] Patients were considered in combined clinical and biological remission if both criteria were met. In addition, changes in anthropometric measurements and laboratory values (including IFX trough levels) were compared before and after switching to CT-P13 at five different timepoints: six months before switching to CT-P13 (-6; baseline), last infusion prior to switching to CT-P13 (-1), at time of switch (0), first infusion after switching to CT-P13 (+1) and six months after switching to CT-P13 (+6). Finally, the occurrence of adverse events during this switch period was recorded.

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STATISTICS

Continuous variables were presented as medians with interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages. For statistical comparison of paired data obtained at the different timepoints, a Wilcoxon signed-rank sum test and a Friedman test were used for continuous variables. A McNemar test was used for paired dichotomous variables. A two one-sided test (TOST) of equivalence for paired samples was performed to evaluate the similarities between the average cumulative IFX dose before and after switching to the biosimilar CT-P13, where the equivalence margin was set at $\delta = 30$ percentage points. For this analysis, the 90% confidence interval of the means between the two products fell within the range from 70-130%, then the products were considered equivalent. P values were calculated 2-tailed and the threshold for significance was set at 0.05. IBM SPSS 25.0 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

PATIENTS' CHARACTERISTICS

Fifty-two pediatric IBD patients received IFX at our tertiary referral center between July 2017 and January 2018 (**supplemental digital figure 1,http://links.lww.com/TDM/A301**). Forty-seven of them received maintenance therapy with the originator Remicade for at least four months. Forty-two of them were eligible for the study as three patients were transferred to the adult department and two patients stopped IFX just before switching to CT-P13 (due to loss of response or a delayed infusion reaction).

CD was diagnosed in 26 patients (61.9%) and UC in 16 patients (38.1%). Patient characteristics are displayed in **table 1**. Median age at the start of IFX therapy was 12.6 (9.4-14.3) years, with a median disease duration prior to starting IFX of 3.5 (2.0-9.0) months.

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Prior to switching to CT-P13, patients were on IFX originator (Remicade) for a median duration of 13.5 (6.8-35.5) months. Six out of the 42 patients (14.3%) initiated Remicade less than six months prior to switching to CT-P13 and as a result of this, had no IFX maintenance trough level or remission status available at that timepoint (but only data starting from the last infusion prior to switch). One patient was lost to follow-up two months after switching to CT-P13 and was defined as a non-remitter.

DATA ON INFLIXIMAB TROUGH CONCENTRATION AND DOSING SCHEDULE

No evidence for significant changes in IFX trough levels occurred at the different timepoints before and after switching from the originator to the biosimilar CT-P13 (see **figure 1**). The median IFX trough level at baseline (six months prior to switching) was 5.7 µg/mL (3.8-9.3) versus 6.5 µg/mL (3.9-8.6) six months after switching (p=0.900).

There was no significant difference between the proportion of patients with subtherapeutic levels (<3 µg/mL) at baseline (n=5/36; 13.9%) or at the last infusion prior to switching to CT-P13 (n= 6/42; 14.3%) and six months after switching to CT-P13 (n=5/41; 12.2%; p=1.000 and p=1.000, respectively). In all five patients with subtherapeutic levels at baseline, the IFX trough level was optimized (>3 µg/mL) by treatment intensification.

During the observation period, one patient developed an infusion reaction associated with low levels of ATIs (19 ng/mL equivalents MA-IFX10F9) six months after switching to CT-P13. This resulted in the discontinuation of the treatment and the patient was switched to adalimumab. A precipitating factor could be that azathioprine was stopped because of combined clinical and endoscopic remission two months prior to the development of the ATI. In the six months period prior to switching to CT-P13, no other Remicade treated IBD patients developed ATI. However, one patient stopped the originator due to a delayed infusion reaction despite no measurable ATI.

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Since all children received pro-active drug monitoring during maintenance therapy, the dosing schedule could be changed. The median overall standardized IFX dose that was administered during the total observational period was not significantly different at baseline [8.0 (6.7-11.4) mg/kg] or at the last infusion prior to switching to CT-P13 [8.0 (6.7-10.8) mg/kg] compared to six months after switching to CT-P13 [8.0 (6.7-13.3) mg/kg; p= 0.050 and p= 0.171, respectively]. In addition, the cumulative IFX dose administered over a six-month period was not significantly different before switching [36.6 (24.0-53.3) mg/kg] compared to after switching to CT-P13 [35.8 (26.7-55.6) mg/kg; p= 0.214]. The p-value derived from the Friedman test analysis for the changes in IFX dosing at the five different timepoints was also not significant (p=0.488). Finally, the two one-sided t-test (TOST) procedure was used to confirm that the average cumulative IFX dose did not change upon switching. The mean overall standardized IFX dose that was administered during the total observational period was equivalent [51.3 (SD 49.3) mg/kg] compared to six months after switching to CT-P13 [53.9 (SD 52.3) mg/kg; p= 0.047], where the equivalence margin was set at δ= 30 percentage points.

EFFICACY OF SWITCHING FROM THE ORIGINATOR TO CT-P13

The proportion of patients who were in clinical remission at baseline (n= 26/36; 72.2%) or at the last infusion prior to switching to CT-P13 (n= 32/42; 76.2%) was not different from the proportion of patients who were in clinical remission six months after switching to CT-P13 [n= 35/42 (83.3%); p= 0.289 and p= 0.508, respectively]. Two patients developed a flare (disease activity was subsequently proven on endoscopy) that needed treatment intensification in the six months after switching to CT-P13. One refractory CD patient remained at a stable disease activity after switching to CT-P13.

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The median PUCAI levels were not significantly altered at the different timepoints before and after switching from the originator to the biosimilar CT-P13 (see **figure 2**). However, the median PCDAI levels improved significantly over time [at baseline: 5.0 (0.0-9.4) vs six months post switching: 0.0 (0.0-3.8), p=0.005; see **figure 2**].

The proportion of patients in biological remission at baseline (n= 24/34; 70.6%) or at the last infusion prior to switching to CT-P13 (n= 29/38; 76.3%) did not significantly differ from the proportion of patients in biological remission six months after switching to CT-P13 [n= 29/38 (76.3%); p= 0.508 and p= 1.000, respectively]. The median CRP or ESR levels were not significantly altered at the different timepoints before and after switching to CT-P13 (see **figure 3**).

The proportion of patients who achieved combined clinical and biological remission at baseline (n= 20/34; 58.8%) or at the last infusion prior to switching to CT-P13 (n= 26/38; 68.4%) did not significantly differ from the proportion of patients who achieved combined clinical and biological remission six months after switching to CT-P13 (n= 26/38 (68.4%); p= 0.344 and p= 1.000, respectively).

DEMOGRAPHIC AND BLOOD CHEMISTRY COVARIATES

Comparison of the different patients' covariates before and after switching to the biosimilar CT-P13 are displayed in **table 2**. There was no evidence for significant changes of patients' biometrics (body weight and BMI) and biomarkers of inflammation (CRP, ESR and albumin level) at baseline or at the last infusion prior to switch in comparison to six months after switching to CT-P13. However, there was a significant improvement over time for patients' height, hemoglobin and platelet count.

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SAFETY

Typically, only mild infections of the upper respiratory tract were reported (38 events in 26 patients in the period six months prior and 25 events in 18 patients in the period six months after switching to CT-P13, p= 0.317). A detailed report can be found in **supplemental digital table 1,http://links.lww.com/TDM/A302**.

One infusion reaction was reported in a CD patient receiving the biosimilar CT-P13, as mentioned previously, which resulted in the discontinuation of the treatment. One CD patient on IFX originator required an ileocecal resection due to penetrating disease. The same refractory CD patient also required hospitalization after the switch due to disease exacerbation. No other serious adverse events were reported.

Discussion

In this study, pediatric patients with IBD were successfully switched from the IFX originator to the biosimilar CT-P13 during maintenance therapy without affecting the efficacy, pharmacokinetics, immunogenicity and safety.

We showed that there were no significant changes observed in IFX trough levels during a one-year observational period resulted from switching to CT-P13. Although patients underwent pro-active therapeutic drug monitoring, the cumulative IFX dose over a six-month period was not significantly altered before and after switching. Our results are consistent with the only two published pediatric studies on this topic.[32-33] These multicenter British and single center South Korean studies were of similar size pediatric populations (n=33 and n=38, respectively), although the latter study does not represent a “real pediatric cohort” since the mean age was 17.5 ± 4.0 years at time of switch.[33] Our data are also in line with previous published adult literature.[16,34-43]

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The second concern was that switching between the IFX originator and the biosimilar CT-P13 could lead to an increased risk of immunogenicity. Since we are dealing with a vulnerable population with little alternative treatment strategies, we cannot jeopardize anti-TNF therapy due to the presence of ATIs.[22] These concerns were unfounded since only one patient had newly detectable ATIs six months after the switch, which occurred rapidly after stopping azathioprine. In the six months period prior to switching to CT-P13, one patient stopped the originator due to a delayed infusion reaction despite no measurable ATIs. The effect of switching on immunogenicity has only been mentioned in three other pediatric studies.[32-33, 44] These data did not reveal an increase in immunogenicity after the switch. In the study of Kang et al. only 1/38 developed ATI >10 AU/mL in the CT-P13 switch group versus 2/36 in the originator group.[33] In the study of Gervais et al., there was no significant change in ATI status after six and 12 months.[32] Richmond et al. reported 2/20 patients with ATI post-induction, one of whom experienced an acute infusion reaction after a drug holiday of six years.[44] Taking into account of all other adverse events from this study and all other published data (including preliminary data), we can conclude that there is a good safety profile.[20-21,45-46]

Switching to the biosimilar CT-P13 during maintenance therapy has led to comparable clinical, biological or combined clinical with biological remission between baseline and six months post-switch (all $p>0.05$). No significant changes in PUCAI score occurred after switching, but there was a statistically significant improvement in PCDAI score between baseline and six months post-switch. It is difficult to assess whether this was a consequence of better therapeutic response to CT-P13 or of a longer treatment time (especially since some patients were switched shortly after entering maintenance therapy where additional therapeutic drug management can improve outcome). Nevertheless, this improvement occurred already before switch and was not clinically important since the median PCDAI

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score dropped from five at baseline to zero six months after switching (PCDAI < 10= remission). This supports that the biosimilar CT-P13 can not only be used in the induction phase[44,47-49] (anti-TNF naïve), but also in the maintenance phase[32-33,50] when patients were switched to CT-P13. In contrast to previous studies, we also looked at biological and combined clinical with biological remission at different timepoints to empower our results.

Finally, we extensively evaluated changes of different clinical and laboratory data that occurred after switching to the biosimilar CT-P13. Overall, no difference was seen in biomarkers of inflammation (CRP, ESR, albumin) and biometrics of patients (weight and BMI), although there was a statistically significant improvement over time for hemoglobin, platelet count and height. However, the hemoglobin and platelet count improvement occurred already before switch and was not clinically relevant. In addition, it is not surprising that there was an improvement of the height after the switch, since a positive catch-up growth can be seen up to two years after induction of IFX (or even beyond).[51] The novelty of this study is that we looked beyond these blood chemistry covariates[32-34] and included also biometrics of the patient.

Although the ESPGHAN Pediatric IBD Porto Group recommended to be cautious when switching to biosimilars,[22] based on increasing amount of real-life data from long-term follow-up studies (including our study), we feel this recommendation should be reconsidered. However, continued pharmacovigilance is still recommended.

The strength of this study is that we were able to extensively evaluate the effect of switching to the biosimilar CT-P13 on different endpoints (efficacy, pharmacokinetics, immunogenicity, patients' biometric and laboratory data) at different timepoints before and after switching. In addition, by including a six-month window prior to time of switch, our patient cohort can be used as its own control group and therefore there will be less confounders between both groups than by comparing IFX biosimilar and originator head-to-

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head in patients. Potential limitations of our study are the relatively small patient population, however, previous published studies have similar size while our cohort is better phenotyped. Additionally, all patients were Caucasian which limits the potential to generalize this data to the whole population. Although we investigated several efficacy endpoints, we did not include data on endoscopic remission or fecal calprotectin to empower our results. ATI presence was measured by a drug sensitive ELISA method instead of a drug tolerant assay, which can measure ATI in the presence of drug enabling an earlier detection compared to the drug sensitive assay. Although, a drug-tolerant assay has failed to show a clinical benefit to a drug-sensitive assay for the management in patients with a stable clinical remission.[52] Finally, by routinely applying therapeutic drug management we could mask potential differences in IFX trough levels related to the switching to CT-P13. However, we could confirm that there is no change in dose optimization upon the switch and that the switching from originator to biosimilar IFX has no clinically relevant impact on therapeutic drug monitoring in standard clinical practice.

In conclusion, we have demonstrated that pediatric IBD patients can be successfully switched during maintenance from the originator to the biosimilar CT-P13. At six months follow-up, there was no significant difference with respect to efficacy, pharmacokinetics, immunogenicity or other patients' covariates.

Abbreviations

ATI: antibodies to infliximab

BMI: body mass index

CD: Crohn's disease

CRP: C-reactive protein

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ELISA: enzyme-linked immunosorbent assay

ESR: erythrocyte sedimentation rate

IBD: inflammatory bowel disease

IFX: infliximab

IQR: interquartile range

PCDAI: Pediatric Crohn's Disease Activity Index

PUCAI: Pediatric Ulcerative Colitis Activity Index

SD: standard deviation

UC: ulcerative colitis

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Figure Legends

Figure 1: p-value derived from the Friedman test analysis for the changes in IFX trough levels at the five different timepoints was 0.316. Note: IFX: infliximab, mo.: month

Figure 2: p-value derived from the Friedman test analysis for the changes in PCDAI and PUCAI at the five different timepoints was 0.097 and 0.563, respectively. However, the median PCDAI levels improved significantly before the switch (p-value between six months prior to versus time of switch=0.019; p-value between six months prior to versus six months after switch=0.005, p-value between last infusion prior to versus six months after switch=0.033).

Note: IFX: infliximab, mo.: month. Timepoints at X-axis: six months before switching to CT-P13 (-6; baseline), last infusion prior to switching to CT-P13 (-1), at time of switch (0), first infusion after switching to CT-P13 (+1) and six months after switching to CT-P13 (+6)).

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Figure 3: p-value derived from the Friedman test analysis for the changes in CRP and ESR at the five different timepoints was 0.223 and 0.272, respectively. CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

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Table 1. Patients' characteristics	
Number of patients	42
Sex, male, n (%)	21 (50)
Crohn's disease, n (%)	26 (62)
Paris classification for CD at diagnosis [53]	
Age at diagnosis, n (%): A1a, A1b	11 (42), 15 (58)
Disease location, n (%): L1, L2, L3	5 (19), 5 (19), 16 (62)
Upper GI involvement, n (%): L4a, L4b	16 (62), 1 (4)
Disease behaviour, n (%): B1, B2, B3	21 (81), 5 (19), 0 (0)
Perianal disease modifier, n (%)	3 (12)
Growth, n (%): G0, G1	18 (69), 8 (31)
Paris classification for UC [53]	
Disease extent, n (%): E1, E2, E3, E4	1 (6), 4 (25), 3 (19), 8 (50)
Disease severity, n (%): S0, S1	11 (69), 5 (31)
Age at diagnosis, year, median (IQR)	11.8 (8.8-13.9)
Age at start of IFX, year, median (IQR)	12.6 (9.4-14.3)
Disease duration prior to start IFX, months, median (IQR)	3.5 (2.0-9.0)
Disease duration on IFX prior to switch, months, median (IQR)	13.5 (6.8-35.5)
Concomitant immunosuppression at time of switch and 6 months post switch, n (%)	18 (43) and 12 (29)
Co-morbidity, n (%): no, arthritis, psoriasis, atopy, PSC	23 (55), 6 (40), 2 (5), 13 (31), 1 (2)
Previous surgery, n (%): hemicolectomy, peri-anal surgery	3(7), 1 (2)
Ethnicity/Race, n (%): Caucasian, non-caucasian	42 (100), 0(0)

Legend: CD: Crohn's disease; GI: gastrointestinal tract; IFX: infliximab, IQR: interquartile range, n: number; PSC: primary sclerosing cholangitis; UC: ulcerative colitis

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Table 2. Comparison of the different patients' covariates before and after switching to the biosimilar CT-P13

Table 2	**Timepoint from switching to the biosimilar CT-P13**			**Comparison between 2 timepoints**	
Covariate	**6 mo. prior (-6)**	**1st IFX prior (-1)**	**6 mo. after (+6)**	**Time: -6 vs +6**	**Time: -1 vs +6**
z-score weight	-0.3 [-1.0-0.3]	-0.2 [-0.8-0.3]	0.0 [-1.0-0.6]	p=0.129	p=0.502
z-score height	-0.5 [-1.4-0.9]	-0.4 [-1.1-0.7]	-0.4 [-1.0-0.5]	p=0.038+	p=0.117
z-score BMI	-1.0 [-1.0-0.6]	0.0 [-0.7-0.5]	-1.0 [-0.7-0.7]	p=0.203	p=0.757
CRP (mg/L)	0.4 [0.3-2.7]	0.6 [0.3-1.2]	0.3 [0.3-1.2]	p=0.219	p=0.367
ESR (mm/h)	8.0 [3.0-23.0]	9.5 [2.0-16.5]	8.0 [2.5-19.0]	p=0.758	p=0.549
Albumin (g/L)	44.3 [40.4-45.4]	44.9 [41.6-46.9]	43.7 [41.6-45.6]	p=0.426	p=0.051
Haemoglobin (g/dL)	12.7 [11.5-13.5]	13.0 [12.2-13.6]	12.9 [12.1-13.7]	p=0.004*	p=0.628
Platelet (10**9/L)	302 [247-383]	300 [254-264]	266 [244-358]	p=0.001°	p=0.006°

Legend:
+The median standard deviation of the length significantly improved from the moment of switch (-0.4 [-1.2-0.7]) till six months after switching to CT-P13 (-0.4 [-1.0-0.5]; p= 0.028).
*The median haemoglobin level significantly improved from baseline (12.7 [11.5-13.5] g/dL) till the moment of switch to CT-P13 (12.9 [11.9-13.6] g/dL; p= 0.001).
°The median platelet count significantly improved from the moment of switch (310 [260-259] 10**9/L) till six months after switching to CT-P13 (266 [244-358] 10**9/L; p= 0.001).
BMI: body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IFX: infliximab, mo.: months.

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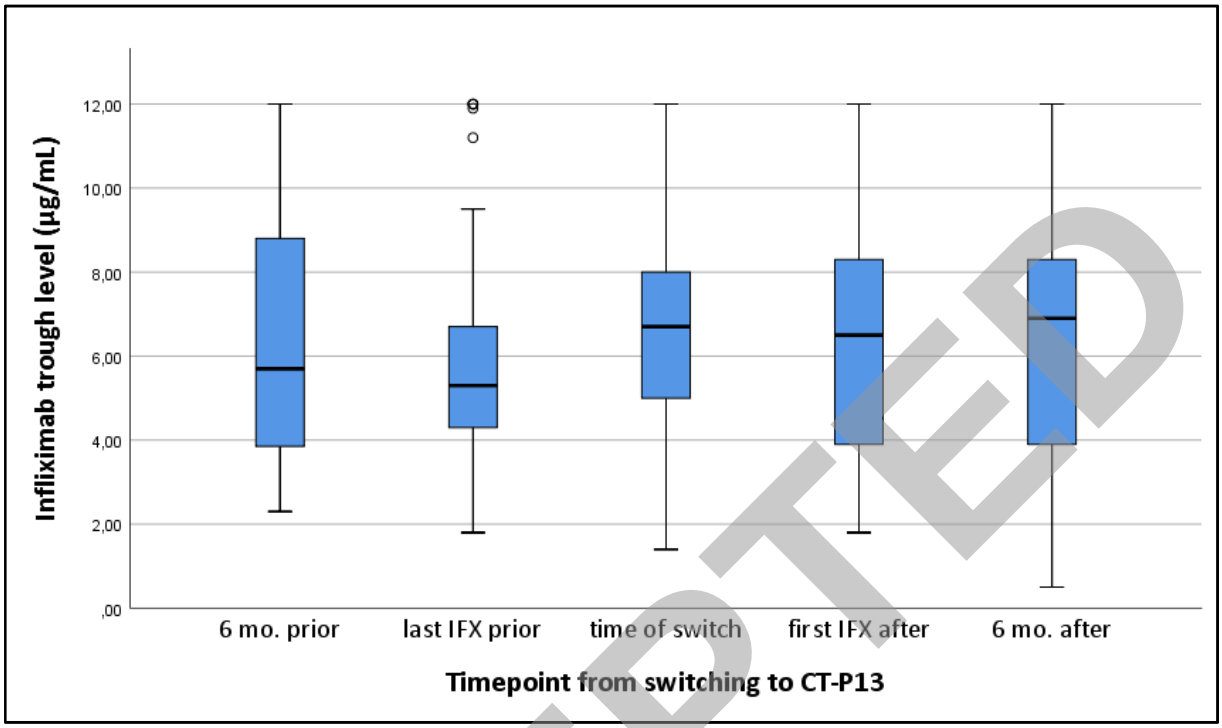
Figure 1. Boxplots showing the distribution of the IFX trough levels at the different timepoints before and after switching from the originator to the biosimilar CT-P13



Legend: p-value derived from the Friedman test analysis for the changes in IFX trough levels at the five different timepoints was 0.316 . Note: IFX: infliximab, mo.: month

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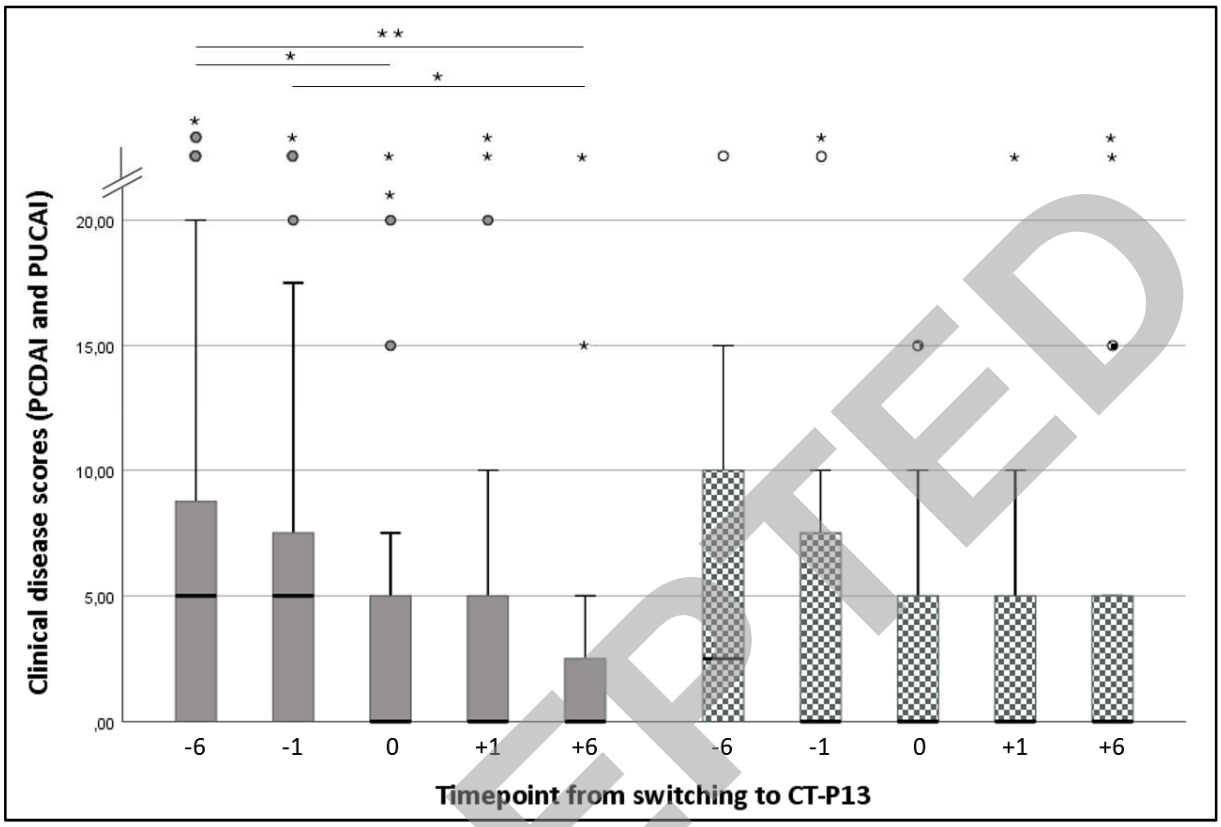
Figure 2. Boxplots showing the distribution of the clinical disease activity scores at the different timepoints before and after switching from the originator to the biosimilar CT-P13



Legend: p-value derived from the Friedman test analysis for the changes in PCDAI and PUCAI at the five different timepoints was 0.097 and 0.563, respectively. However, the median PCDAI levels improved significantly before the switch (p-value between six months prior to versus time of switch=0.019; p-value between six months prior to versus six months after switch=0.005, p-value between last infusion prior to versus six months after switch=0.033).

Note: IFX: infliximab, mo.: month. Timepoints at X-axis: six months before switching to CT-P13 (-6; baseline), last infusion prior to switching to CT-P13 (-1), at time of switch (0), first infusion after switching to CT-P13 (+1) and six months after switching to CT-P13 (+6)).

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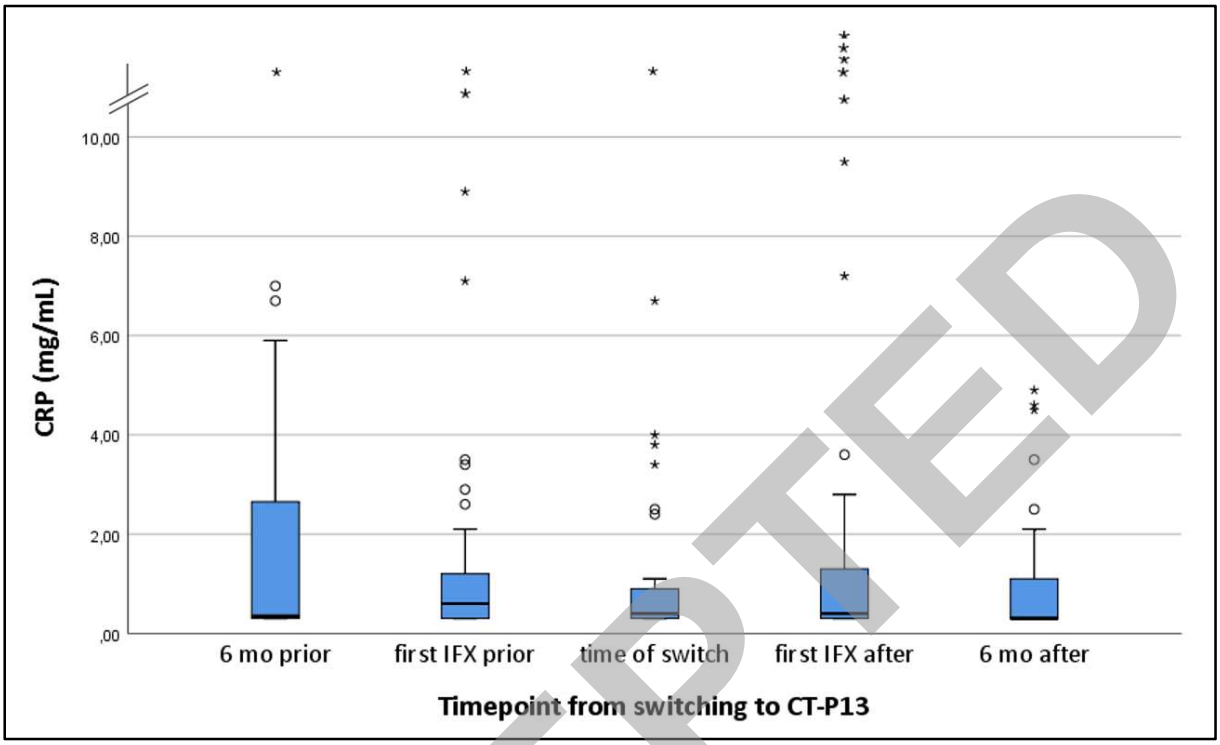
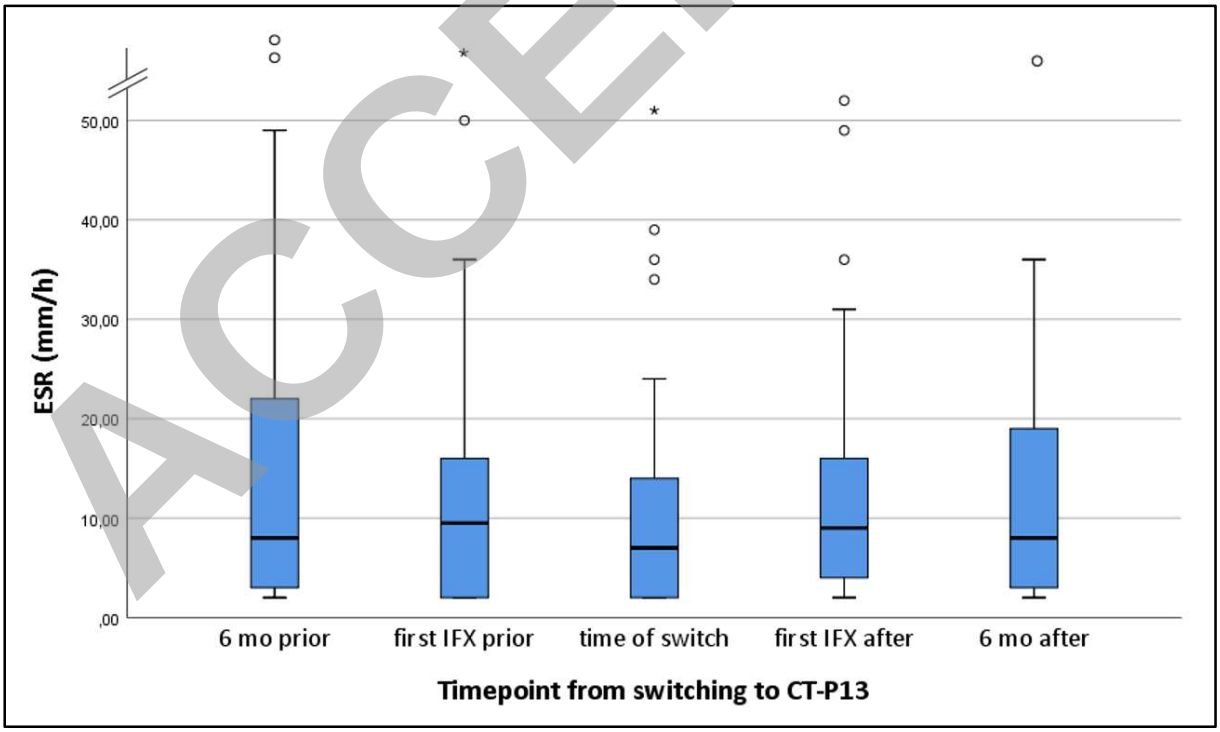
Figure 3. Boxplots showing the distribution of C-reactive protein and erythrocyte sedimentation rates at the different timepoints before and after switching from the originator to the biosimilar CT-P13





Legend: p-value derived from the Friedman test analysis for the changes in CRP and ESR at the five different timepoints was 0.223 and 0.272, respectively. CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

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