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Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease

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Abstract

Background: As the patents of originator biologics are expiring, biosimilar versions are becoming available for the treatment of inflammatory bowel disease (IBD). However, published switch studies of the first infliximab biosimilar, CT-P13, have delivered ambiguous results that could be interpreted as showing a trend towards inferior effectiveness in Crohn's disease (CD) compared with ulcerative colitis (UC). The aim of this study was to investigate the effectiveness and safety of switching IBD patients from treatment with Remicade to CT-P13.

Methods: In this prospective observational cohort study, all adult IBD patients on Remicade treatment, at four hospitals, were switched to CT-P13. The primary endpoint was change in clinical disease activity at 2, 6, and 12 months after the switch. Secondary endpoints were subgroup analyses of patients with and without concomitant immunomodulators; changes in biomarkers, quality of life, drug trough levels and anti-drug antibodies (ADAbs); and adverse events.

Results: A total of 313 IBD patients were switched (195 CD; 118 UC). There were no significant changes in clinical disease activity, quality of life, biomarkers (except a small but significant increase in albumin in CD) including F-calprotectin, drug trough levels, or proportion of patients in remission. Disease worsening rates were 14.0% for CD and 13.8% for UC; and 2.7% developed ADAbs and 2.2% developed serious adverse events.

Conclusions: This is the largest study of switched IBD patients published to date, and it demonstrates that switching from Remicade to CT-P13 may be done with preserved therapeutic effectiveness and safety in both CD and UC.

Keywords: biosimilar, Crohn's disease, infliximab, switch, ulcerative colitis

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Introduction

Infliximab (IFX) is a therapeutic chimeric monoclonal antibody targeting the cytokine tumor necrosis factor α (TNFα). The originator IFX (O-IFX; Remicade®) was approved for treatment of Crohn's disease (CD) in 1998 by the United States (US) Food and Drug Administration (FDA) and in 1999 by the European Medicines Agency (EMA), and for ulcerative colitis (UC) in 2005 and 2006, respectively. The first IFX biosimilar, CT-P13, was approved by the EMA in 2013 and by the US FDA in 2016. When the patent of the O-IFX expired in 2015, CT-P13 could be distributed in Europe.

A biological medicinal product (biologic) is made from living organisms or their products. The EMA defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product'.[1] The use of living organisms in the manufacturing of biologics imposes inevitable variability in the end product. Therefore, unlike chemically synthesized drugs, biosimilars

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are not generic equivalents of the originator product. However, the minor differences that do exist are expected to lack clinical relevance.[2]

Approval of a biosimilar is primarily based on laboratory analyses demonstrating structural and functional similarity to the originator product. In addition, clinical efficacy and safety data in at least one indication are required. These data are then extrapolated across all other indications that the originator product is authorized for. The idea with biosimilars is to provide drugs equally efficacious and safe as the original but at a lower cost, and for this purpose, data extrapolation is fundamental.[2]

The authorization of CT-P13 for CD and UC, collectively named inflammatory bowel diseases (IBDs), involved extrapolation of data from clinical trials in ankylosing spondylitis (AS) and rheumatoid arthritis (RA).[3,4] This has raised controversy, since the efficacy and safety of CT-P13 may differ between IBD and RA/AS.[5,6] Importantly, in the absence of convincing evidence for maintained drug efficacy and safety following a switch, especially with regards to immunogenicity, the feasibility of switching has been a matter of concern in the field.[5]

Larger studies on CT-P13 in IBD patients, especially on switching from O-IFX to CT-P13 during maintenance treatment, have been scarce.[7] However, some real-life data[8–13] and a randomized switch trial (NOR-SWITCH) have been published.[14] Overall, these studies suggest that CT-P13 is efficacious and safe to use in IBD and that switching is feasible.[15] Nevertheless, several pieces of data from these studies have also raised concern regarding the efficacy and safety of CT-P13 in IBD, and thus invoked a need for additional studies.[8–13,16]

The aim of the present study was to assess drug effectiveness, safety, immunogenicity, and drug concentrations, after a nonmedical switch from O-IFX (Remicade) to the biosimilar CT-P13, in a large cohort of IBD patients on maintenance therapy. To our knowledge this is the largest IFX switch study in IBD patients to date.

Materials and methods

Study design and patients

This was a prospective observational open-label multicentre cohort study of a structured nonmedical switch, conducted at four hospitals in the County of Skåne, Sweden. The switch and the follow-up of patients were performed according to a common clinical practice protocol. The patient-specific treatment regimen (i.e. infusion intervals, dosage, and concomitant medication) was not altered in connection with the switch unless clinically indicated. All concomitant IBD therapies were allowed, and dose intensification or de-escalation of 5-aminosalicylates, thiopurines, methotrexate, corticosteroids, or IFX were permitted at the discretion of the treating physician.

All adult patients with IBD on IFX therapy, were consecutively switched from the O-IFX (Remicade) to the biosimilar CT-P13 (Remsima®), starting in October 2015. All patients except one (99.7%) were on maintenance therapy. Each patient received written and verbal information regarding the procedure. The study was performed in accordance with the Declaration of Helsinki and was approved by the regional ethics committee in Lund, Sweden (DNR2017/292). The requirement for written informed consent for data to be used for study purposes was waived by the committee as the switch was part of routine clinical management and the data were analyzed anonymously.

Retrieved patient characteristics data included age at diagnosis, IBD subtype (IBD unclassified was categorized as UC; $n = 5$), IBD phenotype according to the Montreal classification, previous IBD treatment, current medication, and smoking history. Follow-up data (see below for details) were prospectively recorded after the switch, using the Swedish Registry of Inflammatory Bowel Disease (SWIBREG) and medical records.[17]

Study endpoints and assessments

The primary endpoint was change in disease activity at 2, 6, and 12 months after the switch, evaluated by the symptom-based scores Harvey–Bradshaw Index (HBI) for CD[18] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[19] Secondary endpoints were changes in disease activity in patients with and without concomitant immunomodulator treatment; changes in quality-of-life parameters as measured by the Short Health Scale (SHS);[20,21] changes in laboratory biomarkers including C-reactive protein (CRP), hemoglobin (Hb), albumin, and fecal (F) calprotectin; changes in

pharmacokinetics and immunogenicity as measured by serum (S) IFX trough levels and presence of antidrug antibodies (ADAbs), respectively; the proportion of patients in clinical remission and in remission as defined by F-calprotectin, at time points 0, 2, 6, and 12 months; the proportion of patients in remission at baseline (time of switch; representing the status on O-IFX treatment) that had experienced loss of remission (LOR) at the given time points, defined by symptom-based scores and F-calprotectin levels; the proportion of patients with active disease at baseline that had gone into remission at the given time points; and the proportion of patients that experienced disease worsening (DW) at the given time points, irrespective of the patient's level of disease activity at baseline.

Clinical remission was defined as HBI $\leqslant$ 4 for CD and SCCAI $\leqslant$ 3 for UC. Clinical LOR was defined as HBI or SCCAI $\geqslant$ 5 with an increase of $\geqslant$3. DW was defined as an increase of $\geqslant$4 in HBI or SCCAI in combination with HBI or SCCAI $\geqslant$ 7.[14] Achieving remission during follow-up, assessed among patients with active disease (HBI $\geqslant$ 5 or SCCAI $\geqslant$ 4) at baseline, was defined as a decrease of $\geqslant$3 in HBI or SCCAI in combination with HBI $\leqslant$ 4 or SCCAI $\leqslant$ 3.

The SHS is a validated four item (symptom burden, social function, disease-related worry, and general well-being) questionnaire for assessment of health-related quality of life in IBD.[20,21] Each Likert-type item is scored 0–5, where a lower score represents a more positive perception. Adding the scores from the individual items produces a composite score of 0–20.

F-calprotectin was measured by a quantitative enzyme-linked immunosorbent assay (ELISA; PhiCal, Calpro AS) in a routine clinical laboratory. The cut off for remission as defined by F-calprotectin was set to $<$150 μg/g of stool. F-calprotectin LOR was defined as $\geqslant$150 μg/g in combination with an increase of $\geqslant$75 μg/g. Achieved F-calprotectin remission was defined as $<$150 μg/g in combination with a decrease of $\geqslant$75 μg/g.

S-IFX trough concentrations were measured by an ELISA in which IFX bound to TNFα-coated microtiter plates was detected with a labeled Fc-specific antihuman immunoglobulin (Ig)G antibody. The detection limit for S-IFX was $\geqslant$0.2 μg/ml. Values below the detection limit were estimated to 0.1 μg/ml. ADAbs were analyzed by an ELISA based on the inhibition of labeled IFX binding to TNFα-coated wells. This assay is thus drug sensitive and ADAb analysis was limited to patients with undetectable S-IFX. Both ELISAs, previously validated and described, were developed at the Karolinska University Hospital.[22,23]

All adverse events (AEs) considered related or of possible relation to the use of CT-P13 observed in association with the switch or during follow-up were recorded. Serious AEs were defined according to US FDA guidelines.[24]

Statistical analysis

Data are presented as mean (Mn) with standard deviation (SD) or as median (Md) with range or interquartile range (IQR). For comparisons between baseline values and values at time points 2, 6, and 12 months, respectively, the paired samples Student's *t* test was used for interval scale data or where the criteria for a parametric test were met. The Wilcoxon matched pairs signed rank test was used when data failed to meet the assumptions for a parametric test. The Chi-square test for trends was used to examine changes in frequency distribution of SHS subscores. In all analyses, $p < 0.05$ was considered statistically significant.

The number and reason for subject dropouts are presented in the subject flow diagram (Figure 1). Depending on the study design and the causes for missing data points, the missing data imputation method used, can under- or overestimate the therapeutic effect of the study drug. In this study, where 99.7% of patients were on maintenance therapy at baseline, we chose to apply the 'missing equals excluded' (MEX) method[25,26] (equivalent to complete case analysis or per protocol analysis), in combination with an outline of the dropouts in the subject flow diagram. Statistical analysis was conducted with Prism 7 for Mac OS X version 7.0d (GraphPad Software, Inc., La Jolla, USA).

Results

Patients

A total of 313 IBD patients (195 with CD; 118 with UC) were included in the study and switched

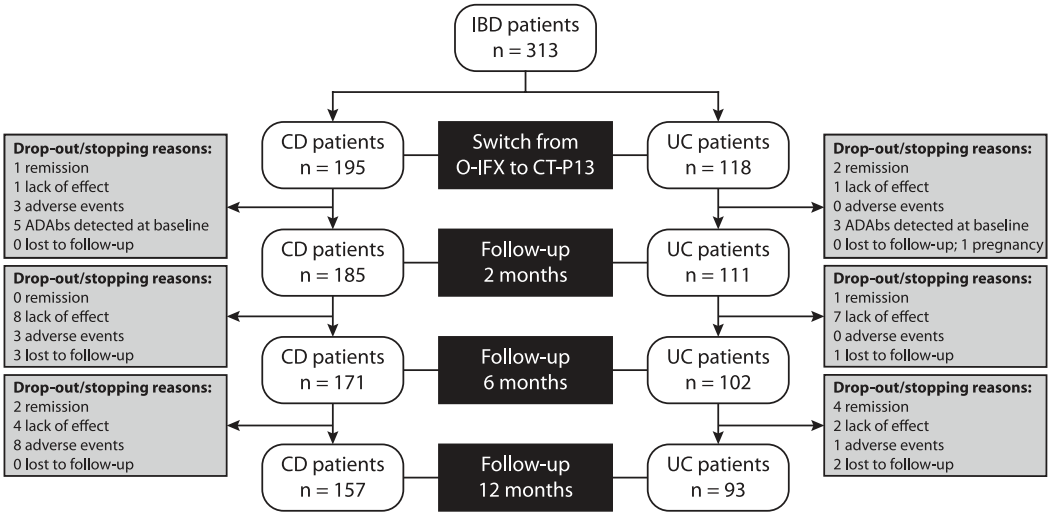

Figure 1. Flow diagram of all patients included in the study. Reasons for stopping CT-P13 therapy or dropout are specified.
ADAbs, antidrug antibodies; CD, Crohn's disease; CT-P13, infliximab biosimilar; IBD, inflammatory bowel disease; *n*, number of participants; O-IFX, originator infliximab; UC, ulcerative colitis.

to CT-P13. The median (range) age at diagnosis was 21 years (6–67) for CD and 27 (6–71) for UC, and at study inclusion 37 (18–78) and 38 (18–78), respectively. The proportion of active smokers was 20.0% among CD patients and 12.7% among UC patients. The phenotypic characteristics according to the Montreal classification are summarized in Table 1. The median time (years; range) for treatment with Remicade prior to switch was 4.6 (0.4–16.6) for CD and 3.6 (0.2–9.6) for UC. During the study, 47.3% received concomitant treatment with thiopurines and 2.9% with methotrexate. Additional information on previous and concomitant IBD therapy is presented in Supplementary Table S1. Overall, 12 months of follow-up was completed by 250 patients (79.9%) (Figure 1). A total of six (1.9%) patients were lost to follow-up due to geographic relocation. CT-P13 treatment was discontinued during follow-up in 10 (3.2%) patients due to remission, 23 (7.4%) patients due to lack of sufficient effect, and 15 (4.8%) patients due to AEs (Figure 1). The proportions of CD and UC patients discontinuing CT-P13 due to lack of effect were similar at 6.7% and 8.5% respectively (Figure 1).

Clinical disease activity

No significant changes in disease activity, measured by HBI in CD and SCCAI in UC, were observed between baseline and the time points 2, 6, and 12 months, regardless of concomitant immunomodulator use [Figure 2(a–d)]. Defined by these scores, 66.2% (100/151) of CD and 71.6% (73/102) of UC patients were in remission at baseline. At 12 months these numbers were 68.2% (73/107) and 78.9% (56/71), respectively. Among CD patients in remission at baseline, 7.6% (7/92), 10.5% (8/76), and 16.9% (11/65) had lost remission at 2, 6, and 12 months, respectively. The corresponding numbers for UC patients were 9.8% (6/61), 11.3% (6/53), and 8.3% (4/48), respectively.

To enable comparison with the NOR-SWITCH study,[14] we performed a calculation of patients that had experienced DW (defined similarly as in the NOR-SWITCH study) at 12 months. The DW rates were 14.0% for CD and 13.8% for UC. In this calculation we defined all the patients that discontinued CT-P13 due to lack of effect as having experienced DW, and subjects that had discontinued CT-P13 due to other reasons as not having experienced DW. Conversely, among patients with clinical disease activity at baseline (33.8% of CD and 28.4% of UC patients), 21.2% (7/33) in the CD and 23.8% (5/21) in the UC group had achieved remission at 12 months (see methods for definitions).

Table 1. Patient characteristics at baseline.

Baseline characteristics	All	CD	UC
IBD diagnosis, *n* (%)	313 (100.0)	195 (62.3)	118 (37.7)
Age at inclusion, Md (range)	37 (18–78)	37 (18–78)	38 (18–78)
Age at diagnosis, Md (range)	24 (6–71)	21 (6–67)	27 (6–71)
Male sex, *n* (%)	211 (67.4)	131 (67.2)	80 (67.8)
Female:male ratio	1:2.1	1:2.0	1:2.1
Montreal classification, *n* (%)			
Age at diagnosis (pertains to CD only, for Montreal classification)			
A1 (<16 years)		52 (26.6)	13 (11.0)
A2 (17–40 years)		115 (59.0)	82 (69.5)
A3 (>40 years)		28 (14.4)	23 (19.5)
Disease location (CD)			
L1 (ileal)		69 (35.4)	
L2 (colonic)		42 (21.5)	
L3 (ileocolonic)		81 (41.5)	
L4 (upper GI)[a]		34 (17.4)	
Disease behavior (CD)			
B1 Uncomplicated		110 (56.4)	
B2 Stricturing		64 (32.8)	
B3 Penetrating		7 (3.6)	
B2B3 Stricturing, penetrating		15 (7.7)	
p Perianal[b]		69 (35.4)	
Disease extent (UC)			
E1 Proctitis			8 (6.8)
E2 Left sided			51 (43.2)
E3 Extensive			59 (50.0)
Smoking status, *n* (%)			
Never	163 (52.1)	101 (51.8)	62 (52.5)
Previous	96 (30.7)	55 (28.2)	41 (34.7)
Active	54 (17.3)	39 (20.0)	15 (12.7)

(Continued)

Table 1. (Continued)

Baseline characteristics	All	CD	UC
Clinical / lab. status at baseline, Mn (SD); Md (IQR)			
Harvey–Bradshaw Index (HBI)		3.44 (3.27); 2 (1–5)	
Simple Clinical Colitis Activity Index (SCCAI)			2.75 (2.86); 2 (1–4)
Short Health Scale (SHS) composite score		5.57 (4.14); 5 (3–8)	5.46 (3.84); 5 (3–8)
Hemoglobin g/l		139.3 (13.4); 140 (131–148)	140.1 (13.3); 141 (131–152)
CRP mg/l		3.38 (6.20); 1.6 (0.7–3.7)	2.93 (7.24); 1.0 (0.3–2.0)
Albumin g/l		38.2 (3.8); 39 (36–41)	40.5 (3.4); 40 (38–43)
F-calprotectin μg/g		125.1 (183.5); 45 (15–141)	181.4 (336.6); 32 (12–108)
S-infliximab trough concentration μg/l		4.74 (3.32); 4.0 (2.4–7.0)	5.24 (3.98); 4.4 (2.4–6.9)

[a]May coexist with L1–L3. [b]May coexist with B1–B3.
CD, Crohn's disease; CRP, C-reactive protein; F, fecal; GI, gastrointestinal tract; IBD, inflammatory bowel disease; IQR, interquartile range; Md, median; Mn, mean; *n*, number of participants; S, serum; SD, standard deviation; UC, ulcerative colitis.

Biomarkers of disease activity

Laboratory blood test biomarkers of disease activity (CRP, Hb, and albumin) did not indicate any DW after switch, neither in CD nor in UC [Figures 3(a) and 4(a)]. On the contrary, albumin levels in CD increased significantly over time with a mean change of +0.46 g/l at 2 months; +0.72 g/l at 6 months; and +1.22 g/l at 12 months [(Figure 3(a)]. The results were similar for patients with and without concomitant immunomodulators [Figures 3(b) and 4(b)].

The mean F-calprotectin value in CD was increased at 2 months (mean change of +53 μg/g), but not at 6 and 12 months [Figure 3(a)]. In UC there were no significant changes in F-calprotectin [Figure 4(a)]. The results were similar for patients with and without concomitant immunomodulators [Figures 3(b) and 4(b)]. The proportion of patients in remission at baseline as defined by F-calprotectin was 76.8% for CD and 80.5% for UC. At 12 months these numbers were 67.6% and 70.2%, respectively. The proportion of CD patients in remission at baseline that later experienced LOR, defined by F-calprotectin, was 14.5%, 12.7%, and 22.2%, at 2, 6, and 12 months, respectively. Among UC patients, the corresponding numbers were 14.6%, 26.7%, and 29.2%. Conversely, the proportion of patients with active disease at baseline as defined by a F-calprotectin level of ⩾150 μg/g (23.5% among CD patients; 19.5% among UC patients) that had achieved remission at 12 months was 50.0% for CD and 55.6% for UC.

Health-related quality of life

No changes in mean composite SHS score were observed at 2, 6, and 12 months after switch [Figure 5(a) and (c)]. Furthermore, we found no differences between patients with and without concomitant immunomodulators [Figure 5(b) and (d)]. There were no significant changes in the individual SHS items at any observed time point after the switch [Figure 5(e)].

Therapeutic drug monitoring, pharmacokinetics, and immunogenicity

Drug trough levels did not change significantly during follow-up, neither in CD nor in UC patients

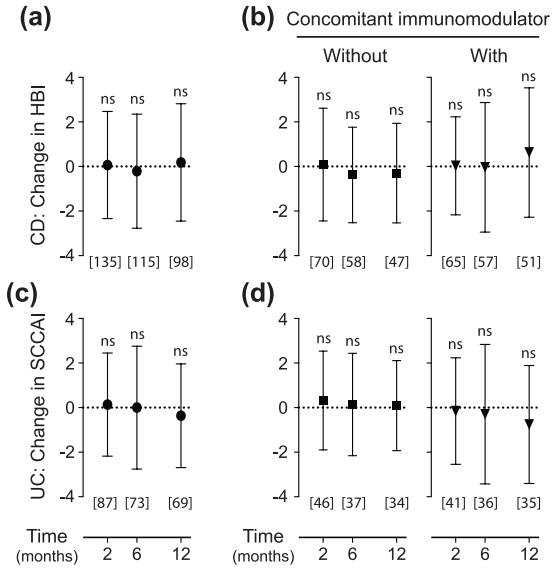

Figure 2. Absolute changes in clinical disease activity scores (HBI for CD patients; SCCAI for UC patients) at 2, 6, and 12 months after switch from Remicade to CT-P13, as compared with baseline (time of switch). (a) CD patients; (b) CD patients, without and with concomitant immunomodulator treatment; (c) UC patients; (d) UC patients, without and with concomitant immunomodulator treatment. The mean (SD) change is plotted at the respective time point. The number of participants (*n*) represented by each data point is indicated in square brackets.
CD, Crohn's disease; CT-P13, infliximab biosimilar; HBI, Harvey–Bradshaw Index; ns, nonsignificant; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; UC, ulcerative colitis.

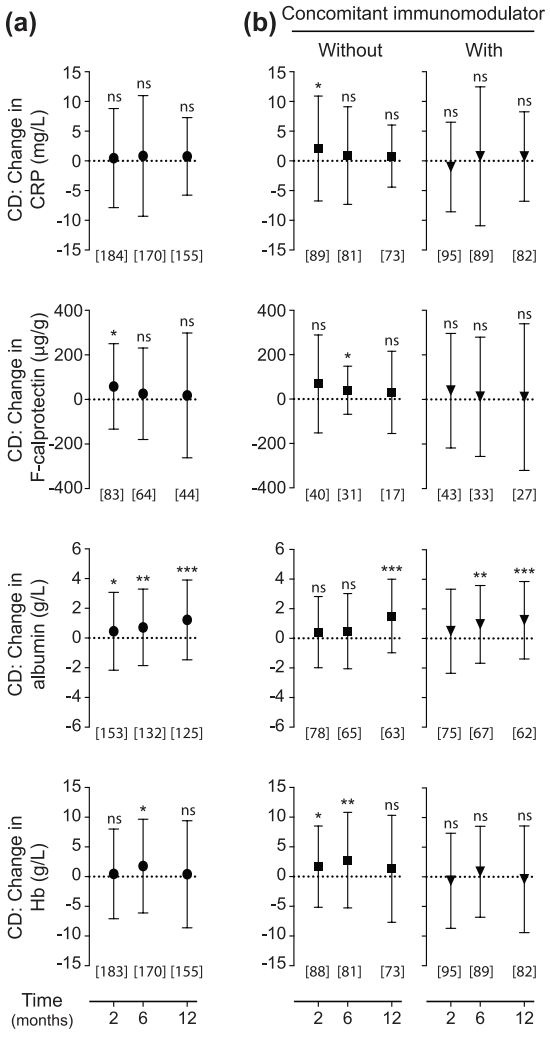

Figure 3. Absolute changes in laboratory biomarkers of disease activity in CD patients at 2, 6, and 12 months after switch from Remicade to CT-P13, as compared with baseline (time of switch). (a) Absolute changes in CRP, F-calprotectin, albumin, and Hb, at 2, 6, and 12 months after switch. (b) Corresponding values subdivided into those without and with concomitant immunomodulator treatment. The mean (SD) change is plotted at the respective time point. The number of participants (*n*) represented by each data point is indicated in square brackets.
ns, nonsignificant; $p \geq 0.05$; *$p < 0.05$; **$p < 0.01$; and ***$p < 0.001$.
CD, Crohn's disease; CRP, C-reactive protein; CT-P13, infliximab biosimilar; F, fecal; Hb, hemoglobin; ns, nonsignificant; SD, standard deviation.

[Figure 6(a) and (c)]. Furthermore, drug trough levels did not differ significantly between patients with and without concomitant immunomodulators [Figure 6(b) and (d)]. ADAbs were detected in six CD (3.2%) and two UC patients (1.8%) that were ADAb negative at inclusion. Analyzing the 250 patients that had a complete follow-up of 12 months, the mean ± SD infliximab dose before switch was 0.86 ± 0.31 mg/kg/week, and after 12 months 0.93 ± 0.38 mg/kg/week. Dose escalation was performed due to increased disease activity in 6.8% (17/250) of the patients during the study; due to low drug levels without signs of increased disease activity in 16.0% (40/250); and in 2.8% (7/250) of the patients there was no documentation on the reason; however, these patients did not show signs of increased disease activity. Drug doses were de-escalated in 12.4% (31/250) of the patients. Of note, many treating physicians in our region had not incorporated proactive therapeutic drug monitoring in their clinical routine at the time of the study. Thus, the 40 patients that were dose escalated due to low drug levels, although being asymptomatic, had in essence, developed low drug levels while treated with the originator product but not revealed as having low drug levels until subjected to the switch protocol

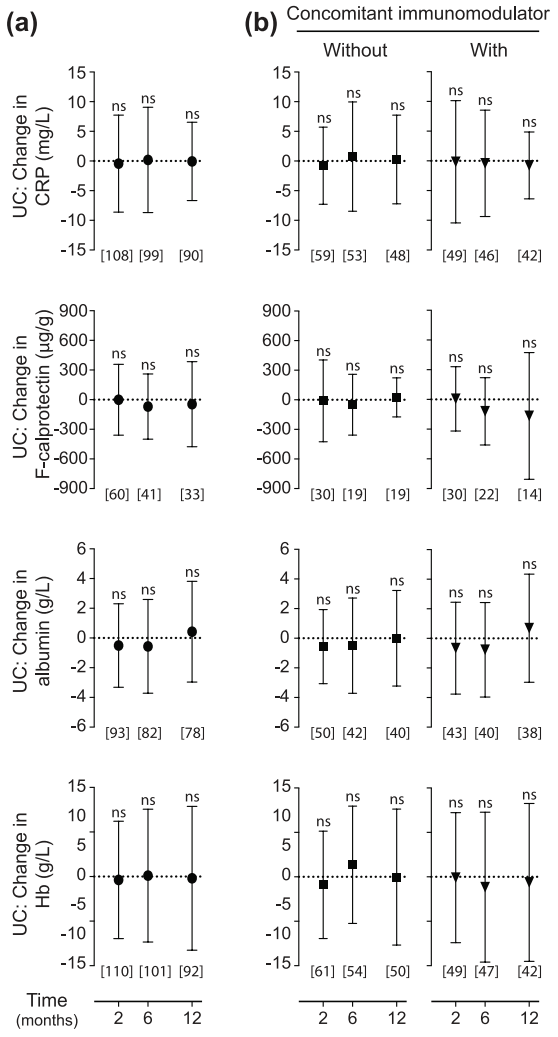

Figure 4. Absolute changes in laboratory biomarkers of disease activity in UC patients at 2, 6, and 12 months after switch from Remicade to CT-P13, as compared with baseline (time of switch). (a) Absolute changes in CRP, F-calprotectin, albumin, and Hb, at 2, 6, and 12 months after switch. (b) Corresponding values subdivided into those without and with concomitant immunomodulator treatment. The mean (SD) change is plotted at the respective time point. The number of participants (*n*) represented by each data point is indicated in square brackets.
CRP, C-reactive protein; CT-P13, infliximab biosimilar; F, fecal; Hb, hemoglobin; ns, nonsignificant; SD, standard deviation; UC, ulcerative colitis.

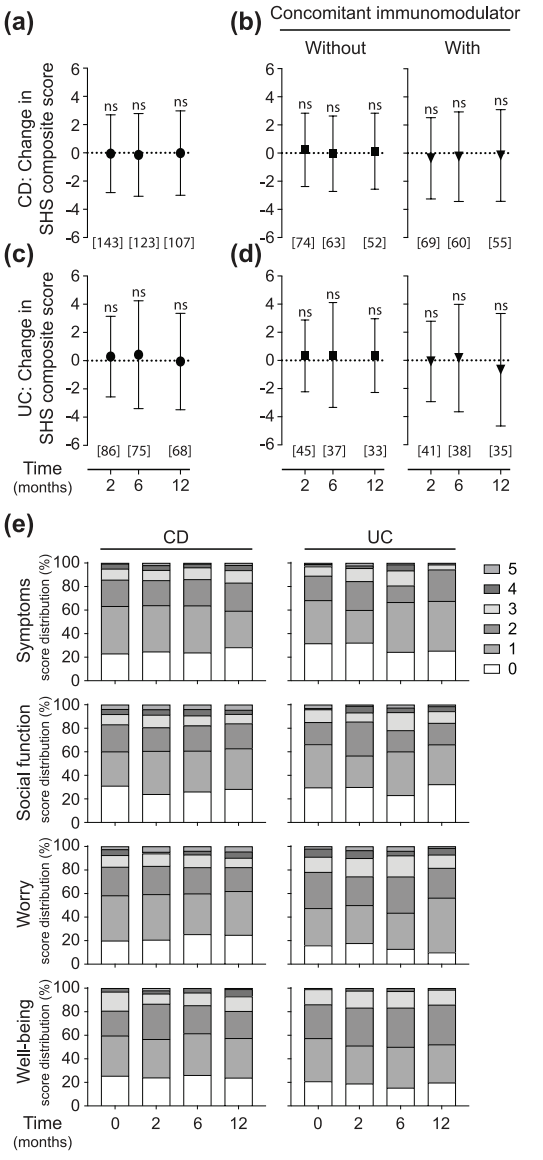

Figure 5. Quality of life measured by the Short Health Scale (SHS) after switch. (a–d) Absolute changes in health-related quality of life measured by the SHS in CD and UC patients at 2, 6, and 12 months after switch from Remicade to CT-P13, as compared with baseline (time of switch). (a) CD patients; (b) CD subgroups without and with concomitant immunomodulator treatment; (c) UC patients; (d) UC subgroups without and with concomitant immunomodulator treatment. The mean (SD) change is plotted at the respective time point. The number of participants (*n*) represented by each data point is indicated in square brackets. (e) Distribution of the SHS subscores (0–5; 0 represents best and 5 represents worst) for each SHS item (symptom burden, social function, disease-related worry, and general well-being), at baseline (time of switch) and 2, 6, and 12 months after the switch.
CD, Crohn's disease; CT-P13, infliximab biosimilar; ns, nonsignificant; SD, standard deviation; SHS, Short Health Scale; UC, ulcerative colitis.

which included measurements of drug concentrations irrespective of symptom levels.

Adverse events

AEs of any type occurred in 47/195 (24.1%) patients with CD and 25/118 (21.2%) patients

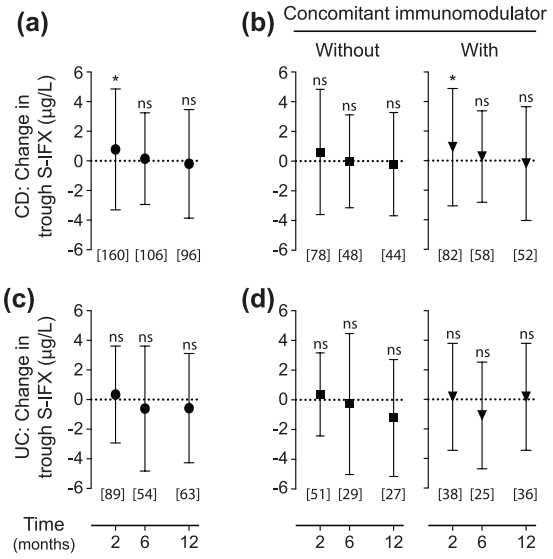

Figure 6. Serum infliximab trough concentrations after switch. (a–d) Absolute changes in serum infliximab trough concentrations in CD and UC patients at 2, 6, and 12 months after switch from Remicade to CT-P13, as compared with baseline (time of switch). (a) CD patients; (b) CD subgroups without and with concomitant immunomodulator treatment; (c) UC patients; (d) UC subgroups without and with concomitant immunomodulator treatment. The mean (SD) change is plotted at the respective time point. The number of participants (*n*) represented by each data point is indicated in square brackets. ns, nonsignificant; $p \geq 0.05$; $^{*}p < 0.05$.
CD, Crohn's disease; CT-P13, infliximab biosimilar; IFX, infliximab; ns, nonsignificant; S, serum; SD, standard deviation; UC, ulcerative colitis.

with UC. In 15 (4.8%) cases, in total, AEs led to CT-P13 discontinuation (Figure 1). AEs reported by at least two patients are presented in Supplementary Table S2. Rash, fatigue, arthralgia, and headache were the most common, with rates of 1.6 to 7.7% (Supplementary Table S2). The number of serious AEs during follow-up was seven (2.2%) in total (Supplementary Table S2). Infusion-related reactions (pruritus, rash, arthralgia, or generalized body aches) occurred in 3/195 (1.5%) patients with CD and 5/118 (4.2%) patients with UC (Supplementary Table S2).

Discussion

This study reports the outcomes of switching from Remicade to the biosimilar CT-P13 in, to our knowledge, the largest cohort of IBD patients described to date (n = 313), with a follow-up time of 12 months. The switch did not result in significant changes in disease activity (evaluated by symptom-based scores and laboratory biomarkers including blood tests and F-calprotectin), health-related quality of life, or serum drug levels. The numbers of AEs and infusion reactions were well within the range of what would be expected with continued O-IFX treatment.[27,28]

Data extrapolation is essential for the cost-effectiveness of biosimilars. Nevertheless, the approval of CT-P13, the first monoclonal antibody biosimilar, for CD and UC without clinical IBD trials has raised criticism. For instance (1) the dominating therapeutic modes of action of IFX seem to differ between IBD and RA/AS (i.e. induction of apoptosis of activated leukocytes *versus* neutralization of soluble TNFα), as illustrated by the lack of effect of etanercept in IBD;[29,30] (2) O-IFX and CT-P13 differ in the fucosylation of glycans on the Fc-portion, in the binding affinity of the Fc-portion to Fc-receptors, and in the antibody-dependent cellular cytotoxicity, which are properties central to the differential modes of action described for IFX above;[5,31] (3) RA and AS are not the most sensitive indications to show potential differences in drug efficacy;[6] (4) there are differences in the propensity for immunogenicity between the various patient populations;[5] (5) there are differences in IFX dosing and immunosuppressive co-medication between the indications, which are relevant for the trials the authorization is based on,[5] and finally; (6) it has been suggested that the 'noninferiority margin' for an equivalence trial in UC patients should be 10% and not 15% which was used in the CT-P13 trials and the NOR-SWITCH study.[32]

In addition to this theoretical basis for concern, emerging data on switching have not been unambiguously reassuring, as well as having indicated that CT-P13 may potentially be less efficacious in CD than in UC. For instance, (1) in the PLANETAS extension study, 71.4% of patients who switched from O-IFX to CT-P13 reported AEs, compared with 48.9% of patients maintained on CT-P13;[16] (2) results from the DANBIO registry (patients with rheumatic diseases) showed that approximately 6% of the patients that were switched from O-IFX to CT-P13 had discontinued treatment already after 3 months due to lack of effect or AEs;[13] (3) the NOR-SWITCH trial was very close to showing that CT-P13, after switching from O-IFX, was significantly inferior in efficacy as compared

with continued treatment with O-IFX, in CD but not in UC;[31,33] (4) in a prospective observational cohort study with 6 months of follow-up after switch in 99 CD and 44 UC patients, Buer and colleagues showed that the proportion of patients in clinical remission decreased from 87% at baseline to 81% after switch in CD patients, but increased from 88% to 95% in UC patients, that the mean F-calprotectin levels (μg/g) increased from 262 to 456 in CD (non-significant; ns) and from 258 to 316 in UC (ns), that the proportion of patients with a F-calprotectin <250 μg/g decreased from around 66–47% for CD and from around 79–75% for UC, that all patients with detectable ADAbs after switch had CD and not UC, and finally, that the 6-month LOR rates were 30% in CD and 27% in UC, which are considerably higher numbers than what has been seen for O-IFX;[8] (5) in another prospective observational cohort study, with approximately 4 months of follow-up after switch in IBD patients, Smits and colleagues showed that the LOR rates were 20% in CD and 16% in UC, which again are rather high numbers given the short time period;[9] (6) a prospective observational cohort study with up to 12 months of follow-up after switch in IBD patients, performed by Argüelles-Arias and colleagues, reported that among patients with CD that were in remission at baseline, 30% had lost remission at 12 months and among patients with UC the number was 19%;[10] and finally, (7) Avouac and colleagues showed, in a population with mixed diagnoses, that approximately 17% had discontinued CT-P13 around 6 months after switch, and that the survival on drug rate was 28.2% better in UC compared with CD.[11]

It should be stressed that other pieces of data in the studies described above, a report on the outcomes of a managed switching programme in patients with IBD,[34] and a small pediatric switch study in IBD[35] suggested no relevant differences between O-IFX and CT-P13. Nevertheless, these concerning data highlight the need for additional and larger studies in IBD. The studies cited, including the NOR-SWITCH study, have each studied between 36–143 switched IBD patients with a follow-up time between 4–12 months. Hence, our study, comprising 313 switched IBD patients with a follow-up time of 12 months, is an important addition, especially given the diverging results from the smaller studies.

In the current study, the momentary cross-sectional proportion of patients in remission at baseline and at 12 months was 66.2% and 68.2%, respectively, in CD, and 71.6% and 78.9%, respectively, in UC. Among the patients that were in remission at baseline, 16.9% of the CD and 8.3% of the UC patients had lost remission at 12 months. However, among those with active disease at baseline, 21.2% of the CD and 23.8% of the UC patients had gained remission at 12 months. Thus, disease activity seems to fluctuate over time, may be somewhat more mobile in CD compared with UC, and additionally, the changes being bidirectional and similar in size may be used to argue that CT-P13 is equivalent in efficacy to O-IFX. The expected annual LOR rates for Remicade are approximately 10–20%,[28,36–38] which is in line with the results from our study on CT-P13. We calculated DW with similar definitions as used in the NOR-SWITCH trial in which DW occurred in 36.5% of CD and 11.9% of UC patients, after 12 months.[14] The corresponding rates in our study were 14.0% for CD and 13.8% for UC, thus contravening a potential inferior effect of CT-P13 in CD.[8,10,11,31,33]

The laboratory biomarkers CRP and Hb did not show significant changes. In CD, albumin increased significantly over the 12 months, suggesting that CT-P13 is not inferior to O-IFX and seems to work equally well in CD and UC. Our analyses of serum drug trough concentrations showed no significant changes compared with baseline, except for a slightly higher mean value at 2 months after switch in CD. We speculated that patients without concomitant immunomodulators could be more prone to develop ADAbs and therefore display a decrease in trough levels. However, the subgroup analysis of patients with and without concomitant immunomodulators did not show any significant differences. One could claim that there was a trend of slightly declining drug concentrations over time, a phenomenon previously described for Remicade.[22] The number of patients where ADAbs developed after switch was low (2.7%) and thus well within the range of what would be expected with continued O-IFX treatment.[22,27,28]

The results regarding AEs were similar to published data on Remicade.[36,37] In the ACCENT I trial (54 weeks maintenance treatment in CD) 11.7% discontinued treatment due to AEs[27] and in the ACT 1 trial (54 weeks maintenance treatment

in UC) the corresponding number was 8.6%.[28] We observed serious AEs in seven cases (2.2%). These were all different and no accumulation of any specific serious AE was noted. The number of infusion-related reactions was low (2.6%), and conforms with our clinical impression that the frequency of infusion reactions with Remicade has decreased over time, which may be related to repeated modifications in the manufacturing process of Remicade.[39] For comparison, the ACCENT I (1999–2001) and ACT 1 (2002–2005) trials reported infusion reactions in 20.8% and 11.1% of patients, respectively.[27,28]

We acknowledge several limitations of the study. Firstly, it did not include a control group continuing treatment with O-IFX. Secondly, the study was not blinded which could affect the subjective read-out parameters. Thirdly, although prospectively recorded some follow-up data, including symptom scores, were missing. Nevertheless, among patients remaining on drug at 12 months, 98–99% had values for important biomarkers such as CRP and Hb, whereas F-calprotectin results (which are dependent on patient-submitted fecal samples) were fewer. Finally, the study did not include endoscopy for evaluation of disease activity.

In conclusion, we have demonstrated that switching from Remicade to CT-P13 may be done with preserved therapeutic effectiveness and safety in patients with IBD. This study is an important contribution to the field, given that (1) the number of switched IBD patients included in this study was more than twice the number in the previously largest study published in combination with (2) that the concerns raised by several previous studies, including a potential difference in the efficacy of CT-P13 in CD compared with UC, were refuted.

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Conflict of interest statement

Leif Angelison has received lecturing fees from Takeda. Olof Grip has received consulting fees from Ferring, Janssen-Cilag, Takeda, and Viphor Pharma. Erik Hertervig has served as a speaker, a consultant, or an advisory board member for AbbVie, Merck, Sharp & Dohme (MSD), and Takeda. Stefan Nilson has served as a consultant for Otsuka. Jan Marsal has served as a speaker, a consultant, or an advisory board member for AbbVie, Bristol-Myers Squibb, EuroDiagnostica, Ferring, Hospira, Janssen-Cilag, MSD, Otsuka, Pfizer, Sandoz, Takeda, Tillotts, and UCB Pharma. Jan Marsal has received investigator-initiated study funding from AbbVie, Ferring, and Pfizer. The other authors have no financial conflicts of interest.

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