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Clinical Outcomes Following a Switch from Remicade® to the Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: A Prospective Observational Cohort Study

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Abstract

Background and Aims: The biosimilar of Remicade®, CT-P13, recently entered the European market. Clinical data on switching from Remicade® to CT-P13 in inflammatory bowel disease [IBD] are scarce. We aimed to prospectively investigate efficacy, safety, pharmacokinetic profile, and immunogenicity following a switch from Remicade® to CT-P13 in IBD patients.

Methods: Remicade®-treated IBD patients at the Radboud university medical centre who switched to CT-P13 were included in this prospective observational cohort study. Primary endpoint was change in Harvey–Bradshaw Index for Crohn's disease [CD] and Simple Clinical Colitis Activity Index for ulcerative colitis [UC] at week 16. We measured C-reactive protein [CRP], faecal calprotectin [FCP], infliximab trough level [TL] and anti-drug antibodies [ADAs] and documented adverse events.

Results: Our cohort consisted of 83 patients (28 males, 57 CD, 24 UC, 2 IBD-unclassified [IBD-U]). The median age was 36 years, range 18–79. Median change in disease activity was 0 [range –23 to +7] for CD and 0 [range –3 to +6] for UC/IBD-U. Median CRP and FCP levels did not change significantly during follow-up. Median TL increased from 3.5 µg/ml [range 0–18] to 4.2 µg/ml [range 0–21] at week 16 [$p = 0.010$]. Two patients developed a new detectable ADA response during follow-up and five patients discontinued CT-P13. No serious adverse events occurred.

Conclusions: We demonstrated that switching from Remicade® to CT-P13 in a real-life cohort of IBD patients did not have a significant impact on short-term clinical outcomes. These results suggest that switching from Remicade® to CT-P13 for the treatment of IBD is feasible.

Key Words: Inflammatory bowel disease; biosimilar; switch

1. Introduction

Monoclonal antibodies targeting tumour necrosis factor α [TNFα] are effective for induction and maintenance of remission in inflammatory bowel disease [IBD] patients.[1] Despite well-accepted efficacy and a reassuring safety profile, the use of infliximab [Remicade®] in daily practice is curtailed due to significant costs. Indeed, anti-TNFα therapy is currently the main cost driver in IBD healthcare.[2] Recently, the patent for Remicade® expired and the biosimilar CT-P13

[Remsima®, Inflectra®] was introduced to the European market. CT-P13 was already approved in 2013 by the European Medicines Agency for the treatment of inflammatory diseases including IBD.[3]

Biosimilars are attractive options for healthcare organizations given their reduced pricing. A prerequisite for European Medicines Agency approval is that biosimilars must demonstrate similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy.[4] Previous randomized controlled trials have demonstrated bioequivalence and therapeutic equivalence for CT-P13 in ankylosing spondylitis and rheumatoid arthritis patients.[5,6] These results were extrapolated to IBD patients for the purpose of approval by regulatory authorities.

The process of extrapolation has been a topic of discussion among physicians and societies as, for example, outlined by the position statement of the European Crohn's and Colitis Organisation.[7] One of the expressed concerns is that the exact downstream effects that are responsible for efficacy of anti-TNF medication in rheumatoid arthritis and in IBD are largely unknown and might act differently. Other concerns include a limited safety database, a different dosing, and a patient population that differs regarding comorbidity and comedication.[8]

Robust clinical data on CT-P13 in IBD patients are scarce. Currently, no randomized controlled trials in IBD patients are available that compared the safety, efficacy, and pharmacokinetic profile of CT-P13 with Remicade®. Few observational cohort studies reported efficacy data after induction therapy with CT-P13 in IBD patients.[9,10,11,12] Very limited data are available concerning Remicade®-treated IBD patients who switched to CT-P13. One small paediatric switch cohort showed comparable safety and efficacy following a switch to CT-P13.[13]

The premise of biosimilars is that they share the same properties as the branded drug to the level that they are completely interchangeable. However, many physicians are reluctant to switch from Remicade® to CT-P13 in view of the lack of evidence on relevant clinical outcomes. Therefore, we aimed to prospectively investigate efficacy, safety, pharmacokinetic profile, and immunogenicity following a switch from Remicade® to CT-P13 in IBD patients.

2. Materials and methods

2.1. Study design

We established a single-centre prospective observational open-label study at the Inflammatory Bowel Disease Centre of the Radboud university medical centre, Nijmegen, a tertiary IBD referral centre in the Netherlands. All IBD patients treated with Remicade® in our centre switched to CT-P13. This switch took place after careful patient counselling while maintaining medical directives as per hospital protocol. Dosing and interval remained unchanged following the switch to CT-P13 unless clinical need dictated therapy adjustments. Follow-up ended at week 16 [±2 weeks] after switching. Dose optimization of CT-P13 and/or courses of corticosteroids were allowed at the discretion of the treating physician, while all changes were documented. Monitoring of the switch to biosimilars followed recommendations on clinical guidance from the national federation of medical specialists.[14] The requirement for informed consent was waived as concluded by the local Medical Ethics Review Committee [2015-#1922].

2.2. Patients

All IBD patients who switched from Remicade® to CT-P13 were eligible for inclusion, regardless of disease activity. Inclusion criteria included a confirmed IBD diagnosis, age ≥ 18 years and infusion of at least one dose of Remicade® prior to switching. Remicade®-naïve patients were excluded. All concomitant IBD therapies, including 5-aminosalicylates, corticosteroids, thiopurines, and methotrexate, were permitted.

2.3. Baseline characteristics

Demographic and clinical data were recorded, including age at IBD diagnosis, IBD phenotype according to the Montreal classification, smoking status, previous surgical resections, and both previous and ongoing exposure to IBD therapies.

2.4. Study endpoints

The primary endpoint was change of disease activity at week 16 [±2 weeks] after switching to CT-P13 relative to week 0. Disease activity was evaluated with the Harvey–Bradshaw Index [HBI] for Crohn's disease [CD] and the Simple Clinical Colitis Activity Index [SCCAI] for ulcerative colitis [UC].[15,16] Secondary endpoints included additional inflammatory, pharmacokinetic, and immunogenicity parameters, as well as quality of life and safety. All [bio]markers were assessed at weeks 0 and 16 [±2 weeks].

2.4.1. Disease activity

Clinical remission was defined as HBI ≤ 4 and SCCAI ≤ 3.[17,18] Other disease activity endpoints included serum C-reactive protein [CRP] and faecal calprotectin [FCP].

2.4.2. Pharmacokinetics and immunogenicity

Infliximab trough levels [TLs] were measured by a previously validated and described enzyme-linked immunosorbent assay from Sanquin Biologics Laboratory [Amsterdam, the Netherlands].[19] As this assay was previously not applied for measuring CT-P13, we first showed that using this assay serum levels of Remicade® and the biosimilar CT-P13 were equally well detected at linear ranges of 2–50 ng/ml and 3–50 ng/ml, respectively. Samples with higher Remicade®, or CT-P13, concentrations were diluted to fit the linear range of the assay. Remicade® and CT-P13 levels of 3.0–7.0 µg/ml were considered to be in the 'therapeutic' range for the purpose of this study.[20,21]

Levels of anti-drug antibodies [ADAs] to infliximab were measured by a previously validated radio-immunoassay [RIA] from Sanquin Biologics Laboratory, which measures the free fraction of serum ADAs in antibody units [AU] per millilitre.[22] To demonstrate that the ADA assay is able to measure antibodies directed against both Remicade® and CT-P13, we used ^{125}I-labelled F[ab′]$_2$ fragments of CT-P13 to detect infliximab ADAs. ^{125}I-labelled F[ab′]$_2$ fragments of CT-P13 did cross-react equally well to anti-CT-P13 antibodies as to F[ab′]$_2$ fragments of Remicade®. Both ^{125}I-labelled F[ab′]$_2$ fragments detected anti-infliximab antibody levels in the range of 12 – 875 AU/ml.

2.4.3. Quality of life

Quality of life was assessed with the short IBD questionnaire [SIBDQ] and the short-form-36 [SF-36]. The SF-36 contains eight subscales that compose two component scores: a physical and a mental component score [PCS and MCS, respectively]. In SIBDQ, questionnaires with more than two missing answers were excluded. In SF-36, questionnaires with one or more missing subscales were excluded.[23,24]

2.4.4. Safety

All adverse events [AEs] were recorded during the course of the study and categorized according to the Office of Human Research Protection. All patients completed a questionnaire regarding general health status and appearance of any possible AE before every

infusion. Suspected adverse reactions were defined as any AE for which there is a reasonable possibility that the drug caused the AE.[25]

2.5. Statistics

Results are reported as median [range minimum–maximum]. Differences between skewed continuous variables at week 0 versus week 16 were analysed with the Wilcoxon matched-pair signed-rank test. McNemar's test was used for any change in nominal data. A p value <0.05 was considered statistically significant. Data from patients who discontinued CT-P13 were recorded according to the 'latest observation carried forward' method.

3. Results

3.1. Patients

We included 83 IBD patients who switched to CT-P13. One additional patient refused switching and was excluded. Patient characteristics are summarized in Table 1. The cohort consisted of 57 CD patients, 24 UC patients, and two patients with IBD-unclassified [IBD-U]. Women represented 66% of the cohort. The median age at inclusion was 36 years [range 18–79] and the median age at time of IBD diagnosis was 25 years [range 8–65]. Thirty-seven patients [45%] had a history of exposure to anti-TNFα therapy prior to their current Remicade® treatment: 13 had used Remicade®, nine adalimumab and 15 had used both agents. Median duration of ongoing Remicade® treatment at start of the study was 25 months [range 1–168]. Concomitant immunosuppressive medication was recorded in 66% [58% thiopurines, 8% methotrexate] and corticosteroids in 10%. Seventy-eight patients completed follow-up and received three or more CT-P13 infusions. In total, five of 83 patients [6%] discontinued CT-P13 during follow-up due to arthralgia [n = 2], loss of response [n = 1], a move abroad [n = 1], and clinical remission [n = 1].

3.2. Disease activity

Median change in disease activity for CD [HBI] and UC [SCCAI] patients was 0 [range –23 to +7] and 0 [range –3 to +6], respectively

Table 1. Patient characteristics at week 0.

Variable	CD [n = 57]	UC/IBD-U [n = 26]
Male:female, n [%]	17:40 [30:70]	11:15 [42:58]
Age at inclusion [years], median [range]	36 [18–70]	41 [18–79]
Body mass index, median [range]	24.5 [15.7–40.4]	24.8 [18.7–34.4]
Age at IBD diagnosis [years], median [range]	22 [8–64]	30 [15–65]
Smoking status, n [%]		
Never	34 [60]	20 [77]
Previous	12 [21]	2 [8]
Current	11 [19]	4 [15]
Primary sclerosing cholangitis, n [%]	0 [0]	0 [0]
IBD type, n [%]		
CD	57 [100]	
UC		24 [92]
IBD-U		2 [8]
Montreal classification CD		
A [1:2:3]	14:35:8	
B [1:2:3], p	18:18:21, 22	
L [1:2:3], L4	4:14:39, 9	
Montreal classification UC/IBD-U		
E [1:2:3]		1:6:19
Prior medication exposure, n [%]		
Thiopurines	36 [63]	19 [73]
Cyclosporin	1 [2]	6 [23]
Methotrexate	16 [28]	1 [4]
Infliximab [Remicade®]	22 [39]	6 [23]
Adalimumab	23 [40]	1 [4]
Vedolizumab	0 [0]	0 [0]
Prior gastrointestinal resections, n [%]	25 [30]	0 [0]
Concomitant medication use, n [%]		
5-Aminosalicylic acid	2 [4]	17 [65]
Corticosteroids	4 [7]	4 [15]
Thiopurines	34 [60]	14 [54]
Methotrexate	7 [12]	0 [0]
Time using Remicade® [months], median [range]	21 [1–168]	26 [1–62]
Time between last treatment with Remicade® and first CT-P13 [weeks], median [range]	8 [4–8]	8 [6–8]
Infusion interval <8 weeks, n [%][a]	13 [23]	3 [12]
Dose >5.5 mg/kg, n [%][a]	9 [16]	0 [0]
Combined interval <8 weeks and dose >5.5 mg/kg, n [%][a]	4 [7]	2 [8]

IBD: inflammatory bowel disease. UC: ulcerative colitis. CD: Crohn's disease. IBD-U: IBD-unclassified. Montreal classification UC/IBD-U: E, extent; E1, proctitis; E2, left-sided colitis; E3, pancolitis. Montreal classification CD: A, age at diagnosis; A1, ≤16 years; A2, 17–40 years; A3, >40 years; B, behaviour; B1, non-stricturing non-penetrating; B2, stricturing; B3, penetrating; p, perianal disease; L, location; L1, ileal; L2, colonic; L3, ileocolonic; L4, isolated upper disease. [a]Higher dose than 'standard' 5 mg/kg every 8 weeks.

[Figure 1]. At week 0, median HBI was 3.0 [range 0–23] and median SCCAI was 1.5 [range 0–11]; this was not statistically different from week 16, when median HBI was 3.0 [range 0–11: p = 0.409] and median SCCAI was 2.0 [range 0–8: p = 0.169]. The proportion of CD/UC patients in clinical remission was 60%/73% at week 0 versus 67%/62% at week 16 [p = 0.481/p = 0.250, n = 57/n = 26]. Of the patients in clinical remission at baseline, 80% [CD] and 84% [UC] maintained remission throughout the study.

Inflammatory biomarkers followed a similar trend as disease activity scores [Figure 2]. Median levels of FCP at weeks 0 and 16 were 52.0 mg/kg [range 5–1400] and 43.0 mg/kg [range 5–2220: p = 0.699, n = 43], respectively. Median levels of CRP did not change during follow-up (1.0 mg/l [range 1–42] and1.0 mg/l [range 1–68: p = 0.417, n = 83]). In addition, leukocyte and platelet counts, and haemoglobin and albumin levels did not change significantly [data not shown].

Additional medication during follow-up was initiated in four patients due to increased disease activity: two CD and one UC patient required corticosteroids and one patient intensified topical tacrolimus for distal colonic CD.

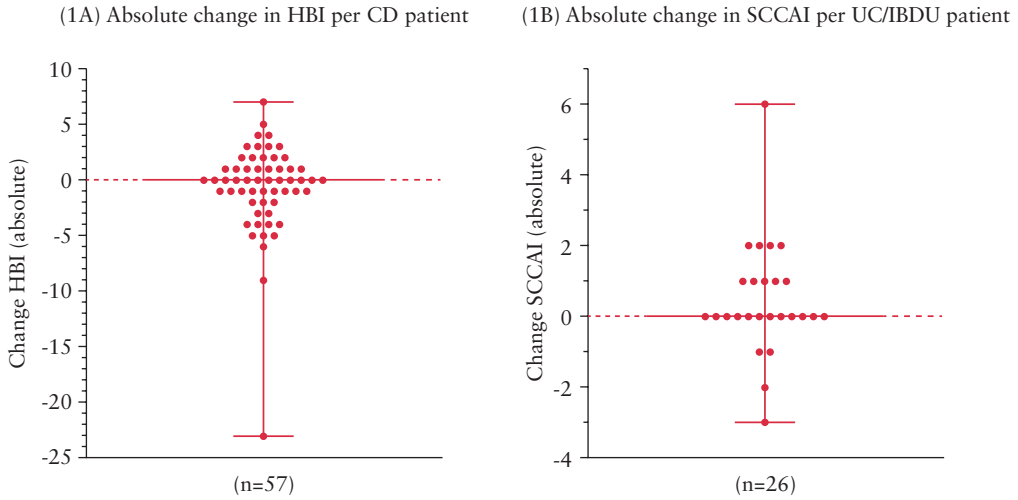

Figure 1. Absolute change in disease activity scores at week 16 relative to week 0, after switching from Remicade® to CT-P13 in inflammatory bowel disease patients. [1A] Harvey–Bradshaw Index [HBI] in CD patients. [1B] Simple Clinical Colitis Activity Index [SCCAI] in UC/IBD-U patients. Absolute change >0: increased disease activity; absolute change <0: decreased disease activity. CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD-unclassified, IBD: inflammatory bowel disease.

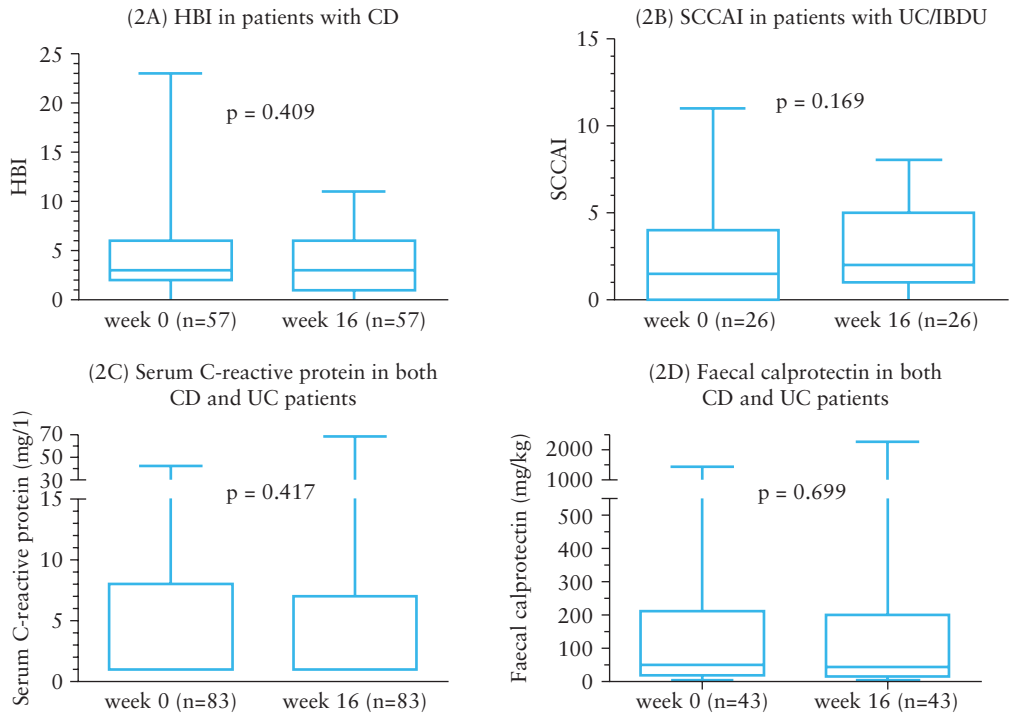

Figure 2. Median [range minimum–maximum] disease activity scores and inflammatory markers at week 0 and week 16 after switching from Remicade® to CT-P13 in inflammatory bowel disease patients. [2A] Harvey–Bradshaw Index [HBI] in CD patients. [2B] Simple Clinical Colitis Activity Index [SCCAI] in UC patients. [2C] Serum C-reactive protein in both CD and UC patients. [2D] Faecal calprotectin in both CD and UC patients. CD: Crohn's disease, UC: ulcerative colitis, IBD: inflammatory bowel disease.

3.3. Pharmacokinetics and immunogenicity

3.3.1. Trough levels

TLs of CT-P13 were not significantly different at week 0 compared to week 16: 3.6 µg/ml [range 0–40] versus 4.2 µg/ml [range 0–21: $p = 0.179$, $n = 83$], respectively. The latter group included five patients who switched from Remicade® to CT-P13 during the induction phase [weeks 0–2–6], which may explain the wide range in TLs at week 0. When we focused on TLs obtained during the maintenance phase, we saw that median TLs were 3.5 µg/ml [range 0–18] at week 0 and 4.2 µg/ml [range 0–21] at week 16 [$p = 0.010$, $n = 73$]. The percentages of patients below, within and above the therapeutic TL range were 44%, 38% and 18% at week 0 and 38%, 42% and 20% at week 16, respectively. CT-P13 dose optimization during follow-up took place in 10 patients with suspected disease activity, including 6/10 patients with low TL. The optimization strategy involved reducing interval spacing [$n = 8$] or dose increase [$n = 2$] at the discretion of the treating physician. Three patients underwent dose reduction during follow-up.

3.3.2. Antidrug antibodies

We found detectable ADAs to infliximab in 7/83 patients [8%] during the study [Table 2 and Figure 3]. This subgroup included five patients who had pre-existing detectable ADA levels at baseline. Two of these five patients had a history of ADA development during adalimumab treatment.

In addition, two patients developed new detectable ADA levels during follow-up. One of the latter patients used concomitant methotrexate and started Remicade® 2 months before switching. The other patient started Remicade® 20 months before baseline and discontinued concomitant azathioprine 10 months before switching because of stable remission.

3.4. Quality of life

SIBDQ scores were available for 63 patients and did not change over the course of 16 weeks: 5.0 [range 2.5–7.0] at week 0 versus 4.8 [range 3.0–7.0, $p = 0.268$] at week 16. SF-36 was assessed in 58 patients. Both physical [PCS] and mental [MCS] component scores remained unchanged from week 0 to 16: PCS 46.7 [range 17.3–63.8] versus 45.9 [range 11.7–59.2: $p = 0.211$] and MCS 50.7 [range 21.7–62.4] versus 49.8 [range 13.4–70.2: $p = 0.718$].

3.5. Safety

All reported AEs during follow-up are listed in Table 3. Twenty-four patients [29%] reported AEs. Suspected adverse reactions occurred in six patients [7%], five patients were able to continue therapy and one patient developed progressive arthralgia after the second infusion with CT-P13 which coincided with continuous high ADA titres. Symptoms resolved after stopping CT-P13. Seven patients [8%] required antibiotics for bacterial infections. Six of these infections had an onset prior to switching to CT-P13. No hospitalization was required.

4. Discussion

This prospective observational cohort study documents clinical outcomes of switching from Remicade® to the biosimilar CT-P13 in a real-life IBD cohort. Switching did not result in significant changes of disease activity as corroborated by relevant and validated biomarkers. Pharmacokinetic parameters such as TLs of CT-P13 were

Table 2. Anti-drug antibodies to infliximab during follow-up.

Case	Diagnosis	T = < week 0		T = week 0		T = week 16		Concomitant medication week 0	Reason for discontinuation	Intervention
		TL	ADA	TL	ADA	TL	ADA			
1	UC	–	–	0.0	18.0	0.0	50.0	5-ASA, budesonide	Progressive arthralgia	Continued co-medication
2	UC	–	–	0.0	37.0	0.0	220.0	5-ASA, AZA	Remission	Continued co-medication
3	UC	–	–	0.5	13.0	0.0	26.0	5-ASA	N/A	Dose escalation to 10 mg/kg
4	CD	0.1[a] / 0.9[b]	14.0[a] / <12.0[b]	0.0[c]	61.0[c]	N/A	N/A	6-TG	Loss of response	Ileal resection
5	CD	–	–	11.0	<12.0	0.0	20.0	MTX	N/A	N/A
6	CD	–	–	1.5	<12.0	0.0	45.0	None	N/A	N/A
7	CD	–	–	0.4	15.0	0.6	16.0	None	N/A	Interval 6 weeks, restart MTX

Data of all 7 patients that showed detectable anti-drug antibodies to infliximab during 16-week follow-up in a cohort of 83 inflammatory bowel disease patients who switched from Remicade® to CT-P13. [a]October 20, 2014; [b]April 7, 2015; [c]week 0: June 2, 2015. TL: trough levels of infliximab [µg/ml], ADA: anti-drug antibodies to infliximab [AU/ml]. ADAs <12.0 AU/ml were considered undetectable. N/A: not applicable. 5-ASA: 5 aminosalicylic acid, MTX: methotrexate, 6-TG: 6-thioguanine, AZA: azathioprine.

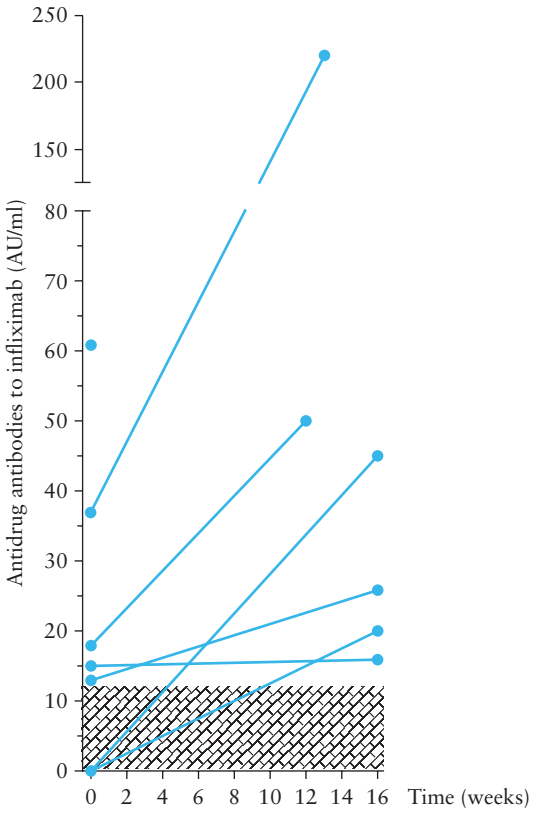

Figure 3. Longitudinal course of antidrug antibodies [ADAs] to infliximab in all 7/83 patients who demonstrated ADAs > 12.0 AU/ml during follow-up. ADAs < 12.0 AU/ml were considered undetectable. One patient [single measurement] had an elevated ADA level at week 0 and discontinued CT-P13 immediately.

Table 3. Adverse events during follow-up

Adverse event	*n*
Fatigue	4
Arthralgia	3
Abdominal pain	3
Progression fistula/bowel obstruction	3
Uveitis	2
Hidradenitis/folliculitis	2
Upper respiratory infection	2
Pyelonephritis	1
Urinary tract infection	1
Leukopaenia	1
Bicytopaenia	1
Progression verrucae vulgares palmare	1
Rosacea	1
Headache	1
Suspected adverse reaction[a]	
Pruritus after infusion	2
Dizziness and tingling sensations after first infusion	1
Warm sensation after second infusion	1
Short period of dizziness after second infusion	1
Arthralgia	1

Reported adverse events during 16-week follow-up in a cohort of 83 inflammatory bowel disease patients who switched from Remicade® to CT-P13.
[a]Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

maintained during the study. Two patients developed new detectable ADAs and five patients discontinued CT-P13.

IBD activity as assessed by HBI and SSCAI remained stable after switching and over 80% of patients maintained clinical remission. Our findings are in line with results seen in conditions with Remicade® maintenance.[26,27,28,29] Similarly, our data on disease activity mirror those of several small studies. A post-marketing study from South Korea reported week 30 data [after switching to CT-P13] in 46 patients and showed that 29/35 CD and 11/11 UC patients did not experience disease worsening.[11] Two retrospective Korean studies showed that switching to CT-P13 resulted in maintenance of remission in 25/27 CD and 6/9 UC patients[30] and in 4/5 CD and 3/4 UC patients.[31]

Note that disease activity as evaluated by symptom-based disease activity scores does not correlate well with mucosal inflammation. Colonoscopy and magnetic resonance imaging would be the preferred diagnostic modalities from a research standpoint, but its routine use is currently not part of clinical care.

We used an RIA for the measurement of ADAs to infliximab. Although this assay was originally validated for Remicade®-specific ADAs, we anticipated that we could use this assay as there was cross-reactivity against CT-P13. Remicade® and CT-P13 share an identical amino acid sequence and a highly similar three-dimensional structure.[32] Indeed, antibodies to Remicade® in sera of IBD patients cross-react with CT-P13, supporting a similar immunogenicity profile.[33] In our cohort, all five patients who had detectable ADAs at baseline [measured prior the first infusion of CT-P13] had detectable ADAs against CT-P13 during follow-up, which may suggest cross-reactivity of ADAs when measured by standardized RIA. In our cohort, two patients developed new detectable CT-P13-specific ADAs during follow-up. In general, ADA assays are less reliable in the presence of detectable TLs.[19] Due to this technical limitation, we cannot exclude the possibility that the newly detected ADAs in these two patients were in fact pre-existing at baseline.

There were no unexpected safety signals during our study, which [to some degree] contrasts with other switch studies. In a cohort of 60 IBD patients, one patient developed a severe infusion-related reaction, while two patients had to discontinue CT-P13 due to a lung abscess [*n* = 1] and an anaphylactic reaction [*n* = 1].[11] A smaller study [*n* = 36] reported that one patient discontinued CT-P13 as a result of a rash and arthralgia.[30] We did not see severe suspected adverse reactions, although two patients stopped CT-P13 because of progressive arthralgia.

Our study has several limitations that need to be addressed. First, the design of the study did not include a control group that allowed patients to continue Remicade®. Therefore, it is difficult to interpret changes in efficacy, safety, and pharmacokinetics that either may be due to the switch to CT-P13 or may be coincident with the natural course. The ongoing NOR-SWITCH study [estimated completion date January 2017] might be able to provide answers to some of the issues. NOR-SWITCH is a randomized, double blind, parallel-group, multicentre study that will report safety and [clinical] efficacy data on switching to CT-P13 relative to continuation with Remicade® in ~500 patients across several indications [ClinicalTrials.gov NCT02148640]. Second, the cohort was heterogeneous in terms of diagnosis, infusion schedule, and disease activity. As such our cohort reflects real-world practice outside the strict inclusion and exclusion criteria of randomized controlled trials, which allows immediate translation of results to clinical care. Third, the duration of follow-up was relatively short. Longer follow-up is required to assess long-term efficacy, safety, and immunogenicity.

In conclusion, we have demonstrated that switching from Remicade® to CT-P13 in a real-life cohort of IBD patients did not have significant impact on short-term clinical outcomes. These results suggest that switching from Remicade® to CT-P13 for the treatment of IBD is feasible.

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Confict of Interest

DJ received consulting fees from Synthon Pharma, Abbvie, and MSD, and travel fees from Falk Pharma, Takeda, Abbvie, MSD, Ferring, Vifor Pharma, and Cablon Medical.

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Author Contributions

LD, FH, JD and LS all contributed to the design of the study. LS collected and analysed the data. FH and LS drafted the manuscript. LD and JD critically revised the manuscript for important intellectual content. DJ and AE provided data and critically revised the manuscript. RB revised the manuscript and added important data regarding the used assays from Sanquin Biologics Laboratory. All authors approved the submitted manuscript.

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