Efficacy and Safety of Elective Switching from Intravenous to Subcutaneous Infliximab [CT-P13]: A Multicentre Cohort Study

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Abstract

Background: Intravenous [IV] infliximab is a well-established therapy for inflammatory bowel diseases [IBD] patients. A subcutaneous [SC] formulation of infliximab [CT-P13] has recently been shown to be as effective as IV infliximab after two doses of IV induction in a randomised trial, but there are no data to support elective switching of patients on maintenance IV infliximab therapy. We aimed to assess the effectiveness of an elective switching programme to SC CT-P13 in patients treated with IV infliximab.

Methods: Patients on established maintenance IV infliximab, who switched to SC CT-P13, were included in this retrospective multicentre cohort study. Disease activity was monitored serially with the Harvey-Bradshaw Index [HBI] for Crohn's disease [CD] and the Simple Clinical Colitis Activity Index [SCCAI] for ulcerative colitis (UC) for up to 12 months at months 3, 6, and 12. Faecal calprotectin [FC] and C-reactive protein [CRP] were recorded at baseline and follow-up, if available. Infliximab trough levels were measured prior to switch and at months 3, 6, and 12 following switch. The primary outcome measure was treatment persistence at latest follow-up. Secondary outcome measures included infliximab pharmacokinetics [PK], safety, need for corticosteroid rescue therapy, and need for surgery.

Results: We included 181 patients, of whom 115 [63.5%] had CD. The majority [72.4%] were on 8-weekly dosing of intravenous infliximab prior to switching, and more than half [59.1%] were on concomitant immunomodulatory therapy. The majority of patients (CD: 106, 92.2%; UC: 46, 76.7%; and IBD unclassified [IBD-U]: 5, 83.3%) were in clinical remission. Treatment persistence rate was high [*n* = 167, 92.3%] and only 14 patients [7.7%] stopped treatment during the follow-up period. There was no significant difference between baseline and repeat measurements at 3, 6, or 12 months for HBI, SCCAI, CRP, or FC. Of the total cohort, 25 patients (13.8%) had perianal CD. Of these, only two patients [8%] had worsening of perianal CD and required antibiotic therapy and further examination under anaesthesia [EUA]. Both these patients also switched back to intravenous infliximab. Median infliximab level increased from a baseline of 8.9 µg/dl [range 0.4-16] to 16.0 µg/dl [range 2.3-16, *p* <0.001] at 3 months. Serum levels stayed stable at 6 months [median 16 µg/dl, range 0.3-17.2] and 12 months [median 16 µg/dl, range 0.3-19.1, both *p* <0.001 compared with baseline]. Among the variables examined, only antibodies to infliximab [ATI] was associated with infliximab levels (odds ratio [OR] -13.369, 95% CI -15.405, -11.333, *p* <0.001). A total of 14 patients [7.7%] developed ATI; of these, nine [64.3%] were on concomitant immunomodulatory therapy. Immunomodulatory therapy was not significantly associated with development of ATI [*p* = 0.15]. In a subset of patients receiving escalated IV infliximab dosing frequency prior to switching, no difference in treatment persistence was observed in patients receiving weekly versus alternate weekly SC CT-P13. Patient acceptance and satisfaction rates with SC CT-P13 were very high.

Conclusions: Among patients on IV infliximab maintenance therapy switched to SC CT-P13, we observed high treatment persistence rates and low rates of immunogenicity, with no change in clinical disease activity indices or biomarkers. Infliximab levels increased after switch to SC CT-P13, and only ATI was associated with serum infliximab levels. Patient acceptance and satisfaction rates were high with SC CT-P13.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; infliximab; anti-tumour necrosis factor antibody; subcutaneous; CT-P13; switch; efficacy

Graphical Abstract

EFFICACY AND SAFETY OF ELECTIVE SWITCHING FROM INTRAVENOUS TO SUBCUTANEOUS INFLIXIMAB (CT-P13): A MULTI-CENTRE COHORT STUDY

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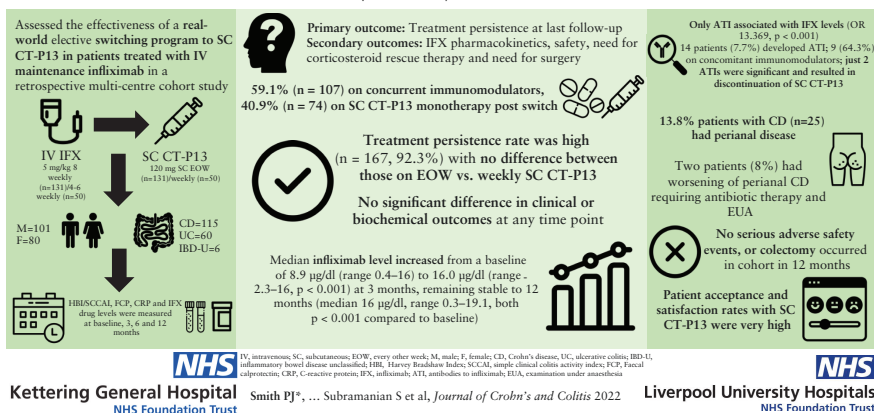
1. Introduction

Infliximab, an intravenously administered chimeric anti-tumour necrosis factor [TNF] antibody, was originally approved for use in inflammatory bowel diseases [IBD] in 1998.[1] Since then, it has been shown to have efficacy across a spectrum of IBD severity and phenotype, and remains the only licensed biologic agent for perianal Crohn's disease therapy.[2] Despite its undisputed efficacy, its use is limited by problems of immunogenicity and intravenous [IV] route of administration. Physicians and IBD patients prefer subcutaneous [SC] therapy to IV therapies, due to ease of use and less utilisation of scant infusion unit resources.[3–5] Moreover, due to the recent COVID-19 [coronavirus disease 2019] pandemic, many intravenously administered biologic agents were either deferred or delayed[6] due to fear of nosocomial acquisition of SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2].

A recent randomised trial evaluated the efficacy and safety of a subcutaneous [SC] formulation of infliximab [CT-P13].[7] Following two induction doses of infliximab, patients were randomised to either SC CT-P13 or IV infliximab. The SC formulation of infliximab was shown to be effective and safe as maintenance therapy for IBD. Intriguingly, the rate of antidrug antibody to SC CT-P13 was consistently lower than that of its IV counterpart, perhaps related to consistent drug exposure as opposed to the peak and trough fluctuations of intravenous therapy.[8] Based on this and a clinical imperative to minimise patient exposure to hospital facilities to mitigate against the risk of nosocomial acquisition of SARS-CoV-2,[9] we initiated a managed switch programme from intravenous to subcutaneous infliximab.[10]

Here, we report on the efficacy, safety, immunogenicity, and pharmacokinetics of elective switching to SC CT-P13 in IBD patients on stable maintenance therapy with IV infliximab.

2. Materials and Methods

We conducted a multicentre study of IBD patients treated with IV infliximab across three hospitals in the UK. Patients on maintenance IV infliximab therapy were eligible to be switched to SC CT-P13. Elective switching to SC CT-P13 was at the joint discretion of patients and physicians. Patients with HBI [Harvey-Bradshaw Index] of <5, an SCCAI [Simple Clinical Colitis Activity Index] of <3 on their first biologic therapy [i.e., infliximab], and on stable dose and frequency of 5 mg/kg maintenance dose for at least 3 months, were targeted for switch initially. All patients had to have started IV infliximab for active luminal disease previously and no patients had had luminal surgery in the previous 6 months. Patients with known antibodies to infliximab, and those who had recent antibiotics and/or examination under anaesthetic [EUA] related to perianal disease in the previous 3 months, were excluded from switching to SC CT-P13. A small number of patients of the overall cohort had HBI [*n* = 9] or SCCAI [*n* = 15] scores above these parameters, but were judged to be clinically quiescent by the initiating investigator because of the presence of concurrent bile salt malabsorption or irritable bowel syndrome [IBS]. Patients were switched to a standard SC CT-P13 dose of 120 mg every other week, but patients on increased dosing frequency of IV infliximab [4- or 6-weekly infliximab] were switched to weekly SC CT-P13 or every other week SC CT-P13, at the discretion of the treating clinician and multidisciplinary team. We collected baseline clinical information including concomitant immunomodulator and steroid therapy, body mass index [BMI], disease extent, HBI, and SCCAI, prior to switch. Follow-up data included HBI, SCCAI, C-reactive protein [CRP], serum infliximab levels, and faecal calprotectin [FCP] [where available] at months 3, 6, and 12 after switch. Data were included if collected within 2-4 weeks of each specified time point. However, infliximab drug levels were all collected within 24 h prior to the next SC CT-P13 injection or, in the case of the first SC CT-P13 dose, immediately prior to this dose. The same drug assays were used in the same patients both before and after switching to SC CT-P13. Patients were excluded if they had not yet completed 3 months of follow-up.

We also recorded details of dose escalation, adverse events and discontinuation of infliximab if they occurred, and need for surgery. Dose optimisation of SC CT-P13 to weekly was based on clinical grounds of suboptimal response combined with biochemical markers of active disease [elevated CRP or faecal calprotectin]. Follow-up was curtailed at 12 months, as the number of patients treated with SC CT-P13 beyond this period was limited. Clinical remission was defined as a HBI of <5 and an SCCAI of <3.[11,12] All patients who had been switched to SC CT-P13 at the largest study site [Royal Liverpool Hospital] were invited to complete a patient

satisfaction survey using an adapted Likert scale questionnaire used in a previous therapeutic switch study.[13]

2.1. Drug level and antidrug antibody assay

Serum infliximab levels and antibodies to infliximab were measured using either a drug-tolerant or a drug-sensitive assay, dependent on the centre from which the patient was recruited. For the drug-tolerant assay, infliximab levels and antibodies were measured by enzyme-linked immunosorbent assay [ELISA] platform, using the Immundiagnostik [Immundiagnostik AG, Bensheim, Germany] IDKmonitor® drug [K9655 for infliximab and K9654 infliximab total antidrug antibody, as previously described].[14] These assays allow quantitative determination of free infliximab using a sandwich ELISA technique. Positive antidrug antibody status was defined in line with the manufacturer's recommendations as a concentration ≥10 AU/mL for the drug-tolerant assay, irrespective of drug level. The IDK assay allows the detection of total antibodies against infliximab; measuring free and bound antibodies against infliximab. The total antibody, unlike the more commonly reported free antibody assay, includes a drug–antibody disassociation step that allows the assessment of antidrug antibodies in the presence of drug. For the drug-sensitive assay, a previously validated in-house ELISA was used to measure infliximab levels and neutralising antibodies.[15] Positive antidrug antibody with the drug-sensitive assay was defined as an antibody titre of 1:40 or greater.

2.2. Outcomes of interest

The primary outcome measure was rate of treatment persistence at latest follow-up. All patients who had at least a 3-month follow-up visit were included in the efficacy analysis. We also assessed infliximab pharmacokinetics [PK] prior to and after switch. We also assessed trends in disease activity indices, faecal calprotectin [FC], and CRP. We recorded details of surgery and adverse events after switching to SC CT-P13 and patient satisfaction with SC CT-P13.

2.3. Patient feedback

Using a Likert scale [1 = strongly disagree to 5 = strongly agree], patients were asked to rate statements related to three main areas: [i] overall satisfaction with SC CT-P13 compared with IV infliximab; [ii] effect of switching to SC CT-P13 on quality of life and ease using SC CT-P13; and [iii] how the patients felt their symptoms/health were controlled on SC CT-P13 compared with IV infliximab.

2.4. Statistical analysis

Descriptive statistics were used to analyse demographic, disease, and treatment characteristics. Categorical variables were summarised as frequency [%] and continuous variables as mean and standard deviation [SD] for normally distributed data, or median and range or interquartile range [IQR] for non-normally distributed data. The Mann-Whitney U test was used to compare differences across medians for non-normally distributed data. Kaplan-Meier survival analysis was used to generate treatment persistence. We used repeated measures analysis of variance [ANOVA] to analyse trends in disease activity indices and to assess changes in FC, CRP, and serum infliximab levels, with Bonferroni correction for multiple analyses. Only patients with complete data at each time point were included for repeated measures ANOVA. A Wilcoxon signed rank test was used to assess change in disease activity

indices and biomarkers from baseline to latest follow-up. Descriptive methods were used to analyse reasons for treatment discontinuation and surgery. Finally, we performed a logistic regression to assess variables associated with treatment persistence, and a linear regression analysis to assess variables associated with serum infliximab levels after switching. We used the mean serum infliximab levels of measurements obtained at 3, 6, and 12 months. Variables were chosen on the basis of clinical relevance and previously published factors associated with serum infliximab levels. All analyses were carried out using SPSS [Version 27.0, Armonk, NY: IBM Corp].

2.5. Ethical standards

The project used anonymised, routinely collected data extracted by clinical teams as part of local quality improvement activities at the participating centres and analysed for the purpose of local audit of compliance with relevant guidance from the National Institute for Health and Care Excellence and to generate benchmarking data for clinical outcome and safety achieved for different agents at the participating centres. Each site registered the biologics audit with their respective institutional audit department and received approval [Clinical Governance registration number: 9869]. As routinely collected data, they are exempt from the need for ethics committee approval in the UK and from the need to take written informed consent. All data were fully anonymised before pooled analysis.

3. Results

3.1. Cohort

We included 181 patients of whom 115 [63.5%] had CD and 101 [58.8%] were men with a mean age of 39.2 [SD 13.9] years. Patients were switched from either IV CT-P13 [Remsima®] or from IV SB2 [Flixabi®] to SC CT-P13, dependent on the centre. A small number of patients were switched from originator IV infliximab [Remicade®] [n = 3]. The majority [72.4%] were on 8-weekly dosing of intravenous infliximab prior to switching to SC CT-P13, and more than half [59.1%] were on concomitant immunomodulatory therapy [Table 1]. The majority of patients [CD: 106, 92.2%; UC: 46, 76.7%; and IBD-U: 5, 83.3%] were in clinical remission based on disease activity indices at the time of switch. Of the 102 patients who had baseline FC values, 85 [46.9%] had a value <250 µg/g and 158 patients [87.3%] had serum CRP values <5mg/L [Table 1]. The median infliximab trough level at the time of switch was 8.9 µg/dl [range 0.4-16]. The median follow-up period was 12 months [range 3-12] and treatment duration was 12 months [range 2-12 months]. The majority [n = 155, 85.6%] were switched to SC CT-P13 every other week and the remainder [n = 26, 14.4%] were switched to weekly SC CT-P13. Of the 131 patients on 8-weekly IV infliximab prior to switch, 129 [98.5%] were switched to every other week SC CT-P13 and two [1.5%] were switched to weekly dosing. Of the 50 patients on 4- or 6-weekly IV infliximab prior to switch, 26 patients [52%] were switched to weekly SC CT-P13 dosing.

3.2. Treatment persistence

In the overall cohort, 14 patients [7.7%] stopped treatment during the follow-up period [Figure 1]. The median duration of treatment in those who stopped was 3 months [range 2-6 months]. The reasons for treatment discontinuation are summarised in

Table 1. Baseline characteristics of patients switched to SC CT-P13.

	All [*n* = 181]	Ulcerative colitis [*n* = 60]	Crohn's disease [*n* = 115]	IBD-U [*n* = 6]
Age, mean [SD]	39.2 [13.9]	40.2 [13.3]	39.0 [14.4]	32.2 [11.8]
Sex, male, *n* [%]	101 [58.8%]	32 [53.3]	67 [58.3%]	2 [33.3%]
BMI kg/m², mean [SD]	27.2 [5.4]	28.2 [5.9]	26.7 [5.0]	27.1 [7.5]
Montreal age classification				
A1 [<16]			28 [24.3%]	
A2 [17-40]			71 [61.7%]	
A3 [>40]			16 [13.9%]	
Disease extent, *n* [%]:				
Ileal [L1]			29 [25.2%]	
Colonic [L2]			39 [33.0%]	
Ileo-colonic [L3]			48 [41.7]	
Upper GI, [L4]			10 [8.7%]	
Behaviour classification, *n* [%]				
B1			57 [49.6%]	
B2			36 [28.7%]	
B3			25 [21.7%]	
Disease extent [UC], *n* [%]				
Proctitis [E1]		3 [5.0%]		
Left-sided [E2]		42 [71.7%]		1 [16.7%]
Pancolitis [E3]		10 [16.7%]		5 [83.3%]
Perianal disease, *n* [%]			25 [21.7%]	
Inter-sphincteric			13 [11.3%]	
Trans-sphincteric			2 [1.7%]	
Supra-sphincteric			1 [0.9%]	
Extra-sphincteric			2 [1.7%]	
5-ASA use, *n* [%]	53 [29.3%]	38 [63.3%]	14 [12.2%]	1 [16.7%]
Concomitant immunomodulator, *n* [%]	107 [59.1%]	33 [55.0%]	70 [60.9%]	4 [66.7%]
Immunomodulator use, *n* [%]:				
6-MP	14 [7.7%]	8 [13.4%]	5 [4.4%]	1 [16.7%]
AZA	82 [45.3%]	23 [38.3%]	56 [48.7%]	3 [50.0%]
MTX	11 [6.1%]	2 [3.3%]	9 [7.8%]	0 [0.0%]
6-TGN levels, mean [SD]	267.5 [118.5]	249.4 [128.4], *n* = 19	271.6 [116.4], *n* = 47	306.0 [108.6], *n* = 4
Infliximab frequency prior to switch:				
8-weekly	131 [72.4%]	48 [80.0%]	78 [67.8%]	5 [83.3%]
6-weekly	34 [18.8%]	5 [8.3%]	28 [24.3%]	1 [16.7%]
4-weekly	16 [8.8%]	7 [11.7%]	9 [7.8%]	0 [0%]
Steroids at baseline, *n* [%]	2 [1.1%]	1 [1.7%]	1 [0.9%]	0 [0%]
HBI, median [IQR]			1.0 [2.0], *n* = 110	
SCCAI, median [IQR]		1.0 [3.0], *n* = 52		1[1.5], *n* = 5
Baseline CRP, mg/L, median [IQR]	2.0 [4.0], *n* = 178	1.0 [1.8], *n* = 59	1.0 [2.0], *n* = 113	1.0 [1.5], *n* = 6
Infliximab trough level, µg/dl, median [IQR]	8.9 [9.8], *n* = 149	9.0 [9.8], *n* = 50	9.8 [9.7], *n* = 93	16.0 [5.5], *n* = 6
Baseline faecal calprotectin, µg/g, median [IQR]	67.5 [143.5], *n* = 102	91.1 [120.3], *n* = 30	97.5 [208.3], *n* = 67	27.0 [10.5], *n* = 5

SD, standard deviation; *n*, number; BMI, body mass index; UC, ulcerative colitis; 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AZA, azathioprine; MTX, methotrexate; 6-TGN, 6-thioguanine; HBI, Harvey-Bradshaw Index, IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; CRP, C-reactive protein.

Table 2. Of note, two patients [1.1%] switched to vedolizumab due to antidrug antibodies and three patients [1.7%] switched back to IV infliximab due to a localised skin rash. Four patients [2.2%] were lost to follow-up during the study period.

3.3. Effect of clinical variables on treatment persistence

We constructed a multivariable model to assess the effect of baseline clinical and biochemical variables on treatment

persistence. None of the variables examined were associated with treatment persistence [Table 3].

3.4. Trends in disease activity indices, CRP, and faecal calprotectin

There was no significant change in HBI or FC from baseline to end of follow-up at 12 months [Table 4]. There was a significant reduction in SCCAI and CRP from baseline to 12 months [Table 4]. However, after correcting for multiple comparisons, there was no significant difference between baseline and repeat measurements at 3, 6, or 12 months for HBI [Figure 2A], SCCAI [Figure 2B], CRP [Figure 2C], or FC [Figure 2D].
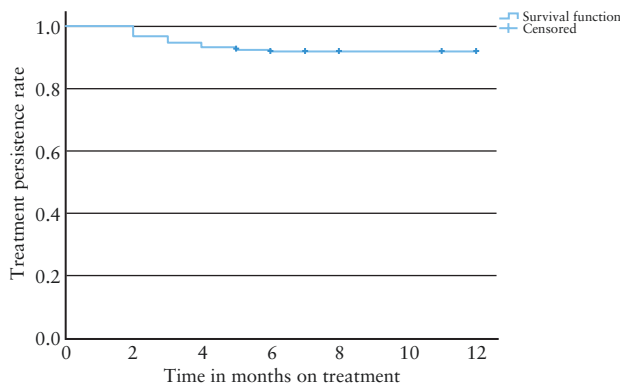
Figure 1. Kaplan–Meier curve of treatment persistence with subcutaneous [SC] infliximab [CT-P13] in patients switching from intravenous infliximab.

Table 2. Reasons for SC CT-P13 discontinuation.

Reason for discontinuation	No. of patients [%]
Worsening of perianal disease	3 [1.7%]
Skin rash	3 [1.7%]
Lost to follow-up	4 [2.2%]
antidrug antibodies	2 [2.2%]
Neuropathy	1 [0.6%]
Worsening of disease activity	1 [0.6%]

SC, subcutaneous.

3.5. Outcomes in IV escalated patients switched to SC CT-P13

Among the 50 patients with escalated IV infliximab frequency at baseline [4- or 6-weekly], we examined if there were any differences in outcomes at 3, 6, and 12 months if they were switched to SC CT-P13 weekly or alternate weekly. There were no significant differences in treatment persistence rates, faecal calprotectin, or infliximab levels between the weekly and alternate weekly dosed patients [Table 5]. There was a significant difference in CRP, with lower CRP values in the weekly group. Of note, patients in the weekly group had a significantly lower CRP at baseline, which persisted through to 12 months [Table 5]. Of note, treatment discontinuation rates at 12 months were not significantly different in the cohort who received 8-weekly IV infliximab [8.4%] compared with those who received escalated dosing frequency of IV dosing [6.0%] prior to switch [$p = 0.59$].

3.6. Outcomes of perianal CD

Of the total cohort, 25 patients [13.8%] had perianal CD. Among patients with perianal disease, four [16%] were switched to weekly SC CT-P13 and the remainder [$n = 21$, 84%] were switched to every other week SC CT-P13. Of these, two patients [8%] had worsening of perianal CD and required antibiotic therapy and further examination under anaesthesia [EUA]. Both these patients also switched back to intravenous infliximab.

3.7. Infliximab pharmacokinetics

The median infliximab level increased from a baseline median of 8.9 µg/dl [range 0.4-16] to 16.0 µg/dl [range 2.3-16, $p <0.001$] at 3 months. Serum levels stayed stable at 6 months [median 16 µg/dl, range 0.3-17.2] and 12 months [median 16 µg/dl, range 0.3-19.1, both $p <0.001$ compared with baseline] [Figure 3].

3.8. Immunogenicity

One patient [0.6%] had antibodies to infliximab [ATI] at baseline despite concomitant immunomodulators, which persisted after switching to SC CT-P13. At 3, 6, and 12 months, a further two [1.1%], one [0.6%] and 11 [6.1%] patients developed ATI, respectively. Among the 14 [7.7%] patients who developed ATI after switch, nine [64.3%] were on concomitant immunomodulatory therapy. Of the 14 ATIs detected, 13 [92.8%] were detected using

Table 3. Effect of clinical variables on SC CT-P13 treatment persistence at latest follow-up.

Variable	Regression co-efficient	95% CI	p-value
UC vs CD	2.068	0.441, 9.696	0.357
Clinically active disease	1.277	0.224, 7.296	0.783
Perianal disease	4.001	0.723, 22.145	0.112
CRP >5 mg/L	0.649	0.072, 5.861	0.700
Dosing regimen [weekly/EOW]	0.625	0.072, 5.411	0.669
Concomitant immunomodulators	0.661	0.183, 2.383	0.527
Antibodies to infliximab	2.102	0.196, 22.523	0.539

SC, subcutaneous; UC, ulcerative colitis; CD, Crohn's disease; EOW, every other week; CI, confidence interval; CRP, C-reactive protein.

Table 4. Trends in disease activity indices, CRP and faecal calprotectin over 12 months from baseline.

Variable, *n.*	Baseline [BL]	3 months	6 months	12 months	*p*-value BL vs 12 months
HBI, median [IQR]	1.0 [2.0], *n* = 110	0.0 [2.0], *n* = 89	0.0 [1.0], *n* = 82	0.0 [1.0], *n* = 78	0.104
SCCAI, median [IQR]	1.0 [3.0], *n* = 57	1.0 [3.0], *n* = 55	0.0 [2.8], *n* = 40	0.0 [4.0], *n* = 41	0.003
CRP mg/L, median [IQR]	4.0 [2.0], *n* = 178	2.0 [1.0], *n* = 159	1.0 [3.0], *n* = 141	2.0 [1.0], *n* = 132	0.008
FC, median µg/g [IQR]	67.5 [143.5], *n* = 102	56.0 [161.5], *n* = 126	67.5 [135.0], *n* = 118	79.0 [138.50, *n* = 117	0.207
Steroid use [%]	2 [1.1%]	1 [0.6%]	0 [0.0%]	0 [0.0%]	

BL, baseline; *n*, number; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; FC, faecal calprotectin.
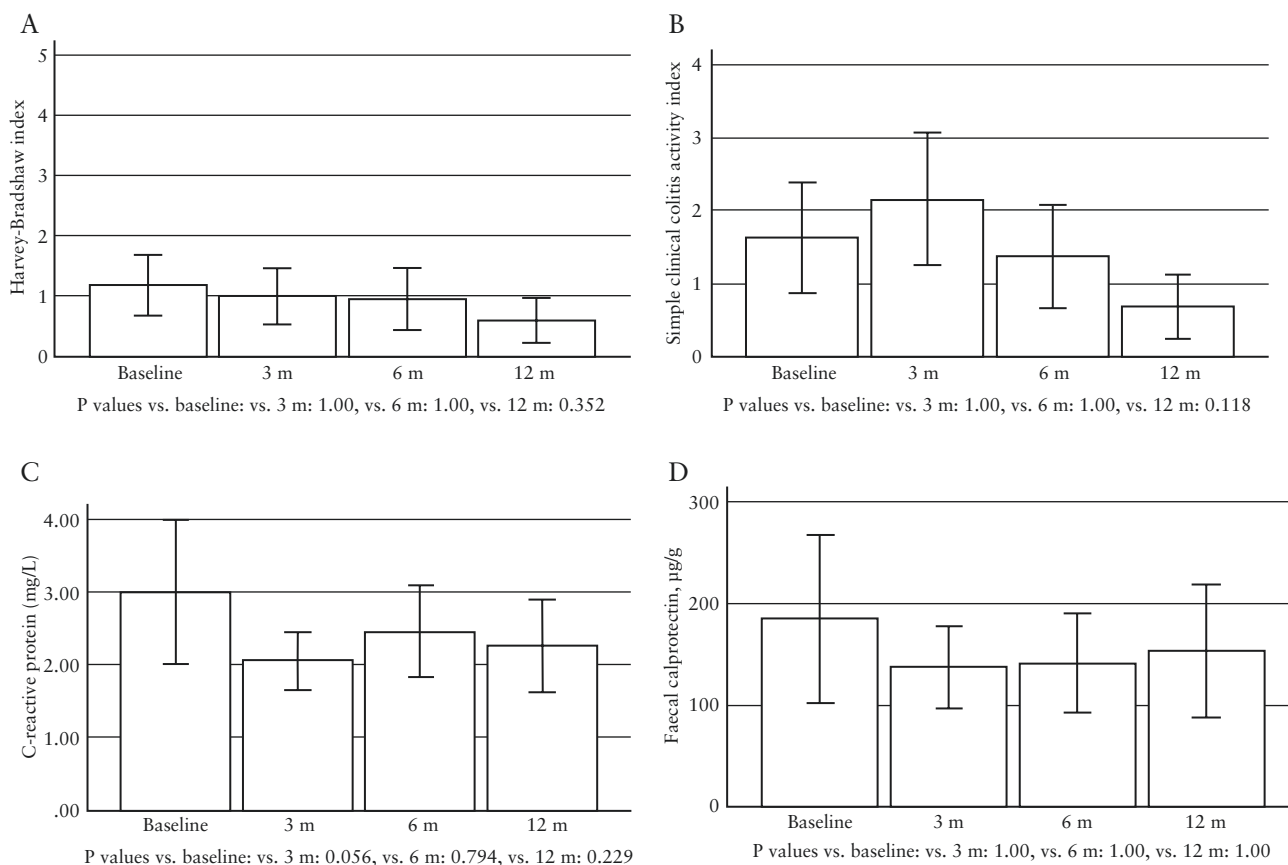

Figure 2. [A] Trends in Harvey–Bradshaw index [HBI] among patients switching to subcutaneous infliximab. HBI was measured at baseline and at 3, 6, and 12 months [m] after switch. Repeated measures analysis of variance [ANOVA] with correction for multiple measures were used to analyse trends. Overall, 63 values were available for comparison across all time points. Bars represent estimated marginal means and error bars represent 95% confidence intervals. [B] Trends in simple clinical colitis activity index [SCCAI] among patients switching to subcutaneous infliximab. SCCAI was measured at baseline and at 3, 6 and 12 months [m] after switch. Repeated measures ANOVA with correction for multiple measures was used to analyse trends. Overall, 32 values were available for comparison across all time points. Bars represent estimated marginal means and error bars represent 95% confidence intervals. [C] Trends in C-reactive protein [CRP] among patients switching to subcutaneous infliximab. CRP was measured at baseline and at 3, 6, and 12 months [m] after switch. Repeated measures ANOVA with correction for multiple measures was used to analyse trends. Overall, 111 values were available for comparison across all time points. Bars represent estimated marginal means and error bars represent 95% confidence intervals. [D] Trends in faecal calprotectin [FC] among patients switching to subcutaneous infliximab. FC was measured at baseline and at 3, 6, and 12 months [m] after switch. Repeated measures ANOVA with correction for multiple measures was used to analyse trends. Overall, 53 values were available for comparison across all time points. Bars represent estimated marginal means and error bars represent 95% confidence intervals.

the drug-tolerant assay. Immunomodulatory therapy was not significantly associated with development of ATI [*p* = 0.15]. Twelve patients [85.7%] remained on SC CT-P13 despite ATI, with the remaining two [14.3%] patients having higher-level ATIs greater than 30 IU/ml. These two patients were both switched to vedolizumab at 3 months post SC CT-P13 switch. Seven patients [50%] who developed ATIs had lower level ATIs less than 30 IU/ml, with five of these patients [71.4%] being on concomitant immunomodulators. All except two patients continued their

SC CT-P13 despite their antibody status. Of the 12 patients who continued their SC CT-P13 therapy, only one had sub-therapeutic levels [0.4 µg/dl] and the remainder had levels >3 µg/dl.

3.9.   Effect of clinical variables on serum infliximab levels

We constructed a multivariable model to assess the impact of clinical and biochemical variables on infliximab levels after switch to SC CT-P13. Among the variables examined, only

Table 5. Treatment persistence rates and biochemical parameters among patients switched to weekly or bi-weekly SC CT-P13 in patients on escalated intravenous infliximab dosing frequency prior to switch.

	Every other week [*n* = 27]	Weekly [*n* = 23]	*p*-value
Treatment persistence rates			
3 months	100%	96.3%	0.353
6 months	92.6%	95.7%	0.357
12 months	92.6%	95.7%	0.650
C-reactive protein [mg/L]			
Baseline	3.0 [4.0]	1.0 [2.0]	0.014
3 months	2.0 [4.0]	1.0 [1.0]	0.019
6 months	2.5 [4.0]	2.0 [1.0]	0.112
12 months	3.5 [4.0]	1.0 [2.0]	0.015
Faecal calprotectin [μg/g]			
Baseline	73.0 [1070.5]	38.0 [125.0]	0.782
3 months	201.0 [193.0]	36.0 [67.0]	0.752
6 months	79.0 [331.5]	49.0 [121.0]	0.476
12 months	183.0 [306.5]	30.0 [86.0]	0.373
Infliximab levels [μg/dl]			
Baseline	11.9 [9.2]	12.4 [8.7]	0.338
3 months	16.0 [2.6]	16.0 [0.0]	0.431
6 months	16.0 [7.3]	16.0 [0.0]	0.909
12 months	16.0 [2.4]	16.0 [0.0]	0.823

SC, subcutaneous.

ATIs was associated with infliximab levels [OR -13.369, 95% CI -15.405, -11.333, *p* <0.001], summarised in Table 6. The remaining variables, including clinically [HBI >5, SCCAI >3] or biochemically CRP >5 mg/L or FC >250] active disease, concomitant immunomodulatory therapy, frequency of SC dosing, and BMI, were not associated with serum infliximab levels.

3.10. Surgery, dose escalation and safety outcomes

Of the entire cohort, three patients [1.6%] were escalated to weekly dosing from every other week dosing. Two patients [1.1%] were hospitalised during the follow-up period for examination under anaesthesia and insertion of seton. There were no recorded intestinal surgeries during the study period. There were no serious adverse reactions to treatment over the 12-month period such as anaphylaxis, severe sepsis episodes, or death. Six patients [3.3%] had self-limiting skin injection reactions. One patient [0.6%] developed paraesthesiae in the arms and legs while on SC CT-P13, subsequently diagnosed as secondary to cervical myelopathy as opposed to a demyelinating aetiology, however they elected to stop SC CT-P13. One patient [0.6%] required oral corticosteroids for worsening UC symptoms after switching to SC CT-P13 [and then discontinued treatment to revert to IV infliximab] but, on review of the patient's history, they had an FC >2100 at baseline and SCCAI score of 11, and so not only did this patient not meet our criteria to switch [so should not have been switched] but it was felt that the switch was highly unlikely to be the cause of the patient's disease activity status. Four patients [2.2%] were lost to follow-up during the study period but had not reported any issues with treatment before it was then discontinued,
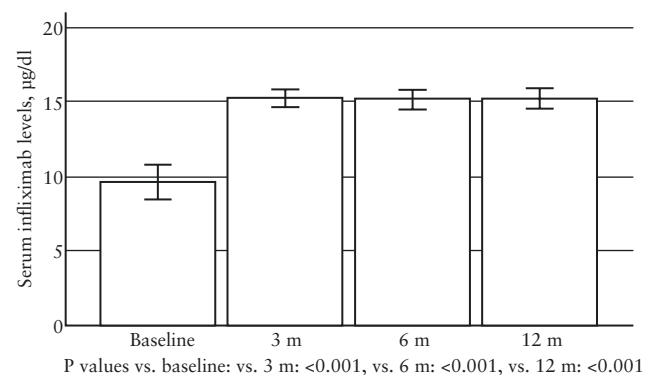

Figure 3. Trends in serum infliximab concentrations among patients switching to subcutaneous [SC] infliximab [CT-P13]. Infliximab levels were measured at baseline and at 3, 6, and 12 months [m] after switch. Repeated measures analysis of variance [ANOVA] with correction for multiple measures was used to analyse trends. Overall, 72 values were available for comparison across all time points. Bars represent estimated marginal means and error bars represent 95% confidence intervals.

with two patients returning to their country of citizenship in Spain and Poland.

3.11. Patient feedback

In all, 88 patients [*n* = 88] completed the patient feedback questionnaire after switching to SC CT-P13; 78.4% [68/88] of patients agreed or strongly agreed that they preferred using SC CT-P13, with 88.6% [78/88] feeling at least the same or better on SC CT-P13. Furthermore, 85.2% [75/88] of patients agreed or strongly agreed that SC CT-P13 treatment was more convenient to their lifestyle than IV infliximab, with 80.7% [71/88] agreeing that SC CT-P13 minimised the negative impact that taking infliximab had on their quality of life, and

Table 6. Effect of clinical variables on serum infliximab levels after switch to SC CT-P13.

Variable	Regression co-efficient	95% CI	*p*-value
Clinically active disease	-0.325	-0.938, 0.288	0.294
CRP >5mg/L	0.480	-0.347, 1.306	0.252
FC >250 µg/g	-0.115	-0.679, 0.449	0.686
BMI	-0.030	-0.072, 0.012	0.162
Dosing regimen [weekly/EOW]	0.316	-0.183, 0.815	0.211
Concomitant immunomodulators	0.045	-0.399, 0.490	0.840
Antibodies to infliximab	-13.369	-15.405, -11.333	<0.001

SC, subcutaneous; CI, confidence interval; CRP, C-reactive protein; FC, faecal calprotectin; BMI, body mass index; EOW, every other week.

92% [81/88] and 86.4% [76/88] agreeing that SC CT-P13 was easy to use and felt safe using it, respectively. Finally, 84.1% [74/88] agreed that SC CT-P13 controlled their condition and symptoms well compared with IV infliximab.

Informal qualitative feedback from the patient interviews was also recorded and highlighted similar themes. In relation to overall satisfaction, patients reported SC CT-P13 as being '…quick and easy to do. I am happy to be on this treatment'; '…I am relatively new on this treatment and I have had no issues. I would like to be on this permanently if no problems emerge'. In the context of quality of life and convenience, feedback included 'I am happy with this treatment as I had to travel far for my infusion previously'; and '…it has been much more convenient for me as I am not local to the hospital'; with some less positive feedback recorded as 'I feel itchy after having the injection but I still prefer it to the infusion'. In terms of disease control, feedback included, 'I was worried at first that this treatment would be less effective but it has been fine'.

4.   Discussion

This study demonstrates for the first time that patients can be electively switched in the real world setting to SC CT-P13 from IV infliximab safely while maintaining clinical remission as well as a high degree of treatment persistence. Infliximab levels significantly increase on initiation of SC CT-P13 compared with IV infliximab, and then plateau, with only the presence of ATI having any effect on SC infliximab levels–consistent with previously published studies on IV infliximab.[16] Interestingly, serum infliximab levels post-switch were not affected by body mass index despite the non-weight based dosing of SC CT-P13. Furthermore, we observed low rates of immunogenicity, and concomitant immunomodulatory therapy did not seem to affect immunogenicity to SC CT-P13. The rate of immunogenicity was lower among SC CT-P13 patients in our cohort compared with previously reported IV infliximab cohorts.[14,17,18] Moreover, most of the patients who developed antibodies had transient non-neutralising antibodies that did not result in treatment discontinuation. This is consistent with previously reported findings that non-neutralising antibodies do not adversely affect outcomes.[19] We also demonstrated that treatment persistence among perianal CD patients is high on SC CT-P13, potentially as a result of the higher infliximab drug levels achieved.[20] Lack of fluctuations in infliximab levels on switching to SC CT-P13 may be protective against the development of immunogenicity previously documented with intravenous infliximab, specially[14,21]

as 'high zone tolerance' to the injected antigen at constant high level–as opposed to extremes of levels–may develop, as seen in other conditions such as rheumatoid arthritis and *in vitro* studies.[22,23]

In our patient cohort, treatment persistence was very high, and would have been higher had four patients not been lost to follow-up during the pandemic. Persistence rates on SC CT-P13 are higher than in other IV infliximab patient cohorts, including those switching to biosimilar drugs.[24–26] Reasons for such a high level of persistence may be the higher therapeutic drug levels we saw or the reduced immunogenicity we have also found in our cohort. It may also be due to more practical matters such as the close virtual follow-up of patients [at baseline, 3, 6, and 12 months] during the COVID-19 pandemic, which may have aided compliance, alongside the need for patients to 'socially distance' to avoid community or nosocomial infection. Certainly, patient feedback has been very reassuring in relation to SC infliximab, which perhaps is an indicator that satisfaction with this therapy may translate into greater compliance and persistence.

The switch to SC CT-P13 appears safe, with no serious adverse events reported and positive patient feedback for switching to SC infliximab in terms of quality of life, safety, control of symptoms, and overall satisfaction, consistent with patients' perspectives on SC medication use in IBD.[13,27,28]

The strengths of our findings include the larger patient numbers in our real-world study than in the original randomised controlled trial which demonstrated SC CT-P13 as an equally efficacious treatment as intravenous infliximab for maintenance in IBD.[7] In addition, our cohort has been followed for 12 months using clinical and biochemical parameters utilised routinely in clinical practice, as opposed to the endoscopic parameters exclusively used in randomised controlled trials, which were not readily available during the COVID-19 pandemic.[29–31] Whereas this is seen as a strength to a real-world study, the pandemic meant that pragmatic decisions had to made to enable social distancing and avoid nosocomial infections, and it could be seen as a limitation despite IBD care being adapted to facilitate safe delivery of care during the pandemic.[32–34] Given the limitations the pandemic placed on health care services in the UK, despite this study being a multisite cohort study there were some data missing at each time point, although not to the detriment of the statistical analysis overall. As an example, access to complete patient surgical notes was limited during the pandemic, meaning we were not able to access whether previous IBD surgery [>6 months previous] had an impact on switch outcomes, but this would be interesting to assess in future

studies. Unfortunately, due to the severe strain the COVID-19 pandemic placed on our gastrointestinal services, our access to endoscopy during the initial months of the pandemic in the UK meant we were only able to endoscope emergent cases such as patients with acute severe colitis.[32] As our patients' needs did not align with our national guidance,[35] we could not assess the degree of intestinal inflammation endoscopically and hence relied on clinical and biochemical markers instead. To ensure social distancing and reduce the risk of nosocomial SARS-CoV-2 infections, IV infusion suites were relocated to exclusively outpatient hospital units away from the frontline inpatient hospitals managing acutely unwell COVID-19 infected patients.

The multisite nature of the study meant the Kettering Hospital used a different infliximab level assay compared with the Liverpool Hospital sites. In Liverpool, the laboratory provider formally tested for ATIs if infliximab levels were less than 0.4 μg/dl, whereas in the assay used by Kettering Hospital, ATIs were measured on every sample. This explains why more low-level ATIs [<30 IU/ml], and likely insignificant ATIs,[36] were detected in this subgroup of patients. Similarly, in the drug-sensitive assay used by Liverpool Hospitals, drug levels were not measured greater than 16. These supratherapeutic levels are not clinically significant, given they are higher than drug level targets for patients with perianal CD, but may in part explain why our perianal CD patients remained well on SC CT-P13.[20,37] Due to limitations on therapeutic drug monitoring and pragmatic decision making during the COVID-19 pandemic, more frequent drug level monitoring was not possible in order to calculate or even model pharmacokinetic and pharmacodynamics data to calculate true 'drug exposure' via the 'area under the curve', but our multivariable regression model clearly demonstrates that only ATIs have an impact on infliximab drug levels[16] even when concomitant immunomodulation is taken into consideration. This is in contrast to previous studies' understanding on the role immunomodulation plays in protecting against ATI development,[14,18] and may suggest monotherapy with SC CT-P13 is less immunogenic compared with intravenous infliximab, although further studies are required. Our study cohort was chosen as stable patients to be switched during for maintenance rather than induction of infliximab treatment during the COVID-19 pandemic, to avoid destabilising more unstable patients at a time of severe health care sector pressure. Therefore we were unable to directly extrapolate our data to more unstable patients or those requiring induction, other than a small number of patients who were escalated to weekly SC CT-P13 or switched to weekly SC CT-P13 from more frequent intravenous infliximab infusions, whose clinical outcomes either improved or remained stable as a result of weekly SC CT-P13. However, further investigation is required to see whether weekly or every other week SC CT-P13 aids the switch from escalated IV dosing. Despite the large sample size, we had only a small number of patients in certain categories e.g. perianal disease, which precluded meaningful interpretation of efficacy in these cohorts.

Concomitant immunomodulators were not stopped during the 12-month study period. In our clinical practice in the UK, in keeping with the findings from the PANTS study,[14] patients have a higher rate of remission at 12 months when on immunomodulators. However, as the immunogenicity of SC CT-P13 needs further investigation, we did not withdraw or introduce immunomodulators during the study period.

We did not have any circumstance to de-escalate SC CT-P13 treatment in patients in this cohort from weekly injections to every other week injections, although potentially longer-term follow-up of patients may provide further insights into whether this is a feasible treatment approach.

Finally, we did not have a comparator cohort of IV infliximab-treated patients to see if treatment persistence rates are comparable across the two groups. Most of the approached patients opted to switch to SC therapy, and thus the IV comparator cohort in our centre would have been too small to estimate treatment persistence in the IV cohort. This could have also introduced a selection bias, as patients who chose to stay on IV administration might have had more severe disease, thus over-estimating the efficacy of SC CT-P13 in our cohort.

In summary, the findings from our real-world study provides strong support for switching stable patients requiring infliximab for maintenance from intravenous to SC CT-P13 electively. With the addition of positive health care economic data, this would provide a very persuasive case for a fundamental landscape change in the way patients are managed on infliximab in the future.

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Conflict of Interest

Author Contributions

All authors were involved in data acquisition. PJS and SS were involved in data analysis and drafting of the manuscript. PJS, SS, AV, CP, AS, ED, PC, MD were involved in drafting and

final revision of the manuscript. PJS and SS were involved in study design, analysis, drafting, and revision of the manuscript. All authors have approved the final version that has been submitted for publication.

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