An observational study of switching infliximab biosimilar: no adverse impact on inflammatory bowel disease control or drug levels with first or second switch

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Summary

Background: Biologics account for a significant cost in inflammatory bowel disease (IBD) management; however, switching from infliximab originator to its biosimilars has enabled cost saving without compromising disease control. The effects on IBD activity and infliximab trough levels of a second switch to another biosimilar are, however, uncertain.

Aims: To assess the effects on disease activity and infliximab trough levels associated with switching from infliximab biosimilar CT-P13 to another biosimilar SB2 and compare outcomes in those switching for the first and second time.

Methods: IBD patients on CT-P13, including some previously switched from originator, were prospectively followed during a switch to SB2. C-reactive protein (CRP), trough infliximab level and clinical disease activity indices were collected at baseline, Infusion 3 or 4 (‘early’ after switch), and 1 year.

Results: One hundred eighty-six patients (n = 99 second switch) on stable infliximab dosing underwent switching. Compared with baseline, there was no significant change in CRP, clinical disease activity scores or median trough infliximab level at the early time point among first-switch (baseline vs early: 5.7 vs 6.6 µg/mL, P = 0.05) and second-switch (4.3 vs 4.9 µg/mL, P = 0.07) patients nor at 1 year (median infliximab trough levels, baseline vs 1 year, in first-switch [5.7 vs 5.7 µg/mL, P = 0.37] and second-switch [4.3 vs 4.7 µg/mL, P = 0.06] patients). The proportion of patients in clinical remission did not significantly change at the early (92% vs 91% at baseline, P = 0.75) or 1 year (95% vs 91% at baseline, P = 0.16) time points. There was no significant difference in time to loss of response between patients switching for the first or second time (P = 0.69).
1 | INTRODUCTION

Biological medicines account for a significant cost to healthcare systems in the management of inflammatory bowel disease (IBD) patients.\textsuperscript{1,2} However, since the expiration of patents for anti-tumour necrosis factor (anti-TNF) originators, biosimilars have offered the possibility of using cheaper alternatives with the potential for marked cost savings.\textsuperscript{3,4}

The original anti-TNF antibody, infliximab (Remicade, Janssen), was authorised in the European Union in 1999.\textsuperscript{5-7} Since then, the biosimilar CT-P13 (Remsima, Celltrion, and Inflectra, Pfizer) has been licenced, followed more recently by others including SB2 (Flixabi, Samsung Bioepis). The regulatory practice of extrapolating the indications for biosimilars to diseases other than that in which the clinical trials established biosimilarity initially caused some controversy.\textsuperscript{8,9} However, subsequent supportive real-world data in IBD\textsuperscript{10} have led to increasing acceptance of this regulatory approach in Crohn's disease (CD) and ulcerative colitis (UC).\textsuperscript{11,12} Furthermore, concerns about initiating biosimilars instead of the originator were relatively rapidly overcome in many countries, perhaps in part driven by the large savings involved.

The practice of switching a patient already established on the originator to a biosimilar, however, raised additional anxieties. The NOR-SWITCH study\textsuperscript{13} provided reassurance that a non-medical switch from originator to biosimilar was not associated with worse outcomes, as was subsequently reported in large real-world datasets.\textsuperscript{4}

With the licencing of more biosimilars, another conundrum has arisen, namely, the effect on disease activity and pharmacokinetics with biosimilar-to-biosimilar switching and particularly with multiple switches. Guidance with respect to interchangeability of biosimilars, encompassing both physician-directed switching and automatic substitution, differs internationally. The European Medicines Agency does not provide specific recommendations with regard to interchangeability, leaving these decisions to the respective countries.\textsuperscript{14} The US Food and Drug Administration (FDA), meanwhile, separates the establishment of biosimilarity from biosimilar interchangeability, with strict trial requirements necessary to meet their criteria for interchangeability.\textsuperscript{15} As a result, no biosimilars have been granted interchangeability status by the FDA thus far.\textsuperscript{16} However, even without designation of interchangeability, US states are able to institute switching and substitution policies for non-medical reasons.\textsuperscript{16}

Limited data exist on biosimilar-to-biosimilar or multiple switches. An observational study of switching from biosimilar CT-P13 to SB2 in IBD is underway (iBiSS, EudraCT Number 2018-001546-33), with promising preliminary results.\textsuperscript{17} Regarding multiple switches, the recent EGALITY study showed equivalent safety, efficacy and immunogenicity comparing continuation vs multiple switches between etanercept originator and a single biosimilar in plaque-type psoriasis.\textsuperscript{18} However, no studies have looked at both pharmacokinetic and clinical outcomes associated with multiple switches between different forms (originator and biosimilars) of a biologic, this being particularly relevant with infliximab, a molecule recognised for its immunogenicity. With the development of new biosimilars and the potential for additional cost savings with multiple switches, this is increasingly relevant.

In 2016, our institution underwent a non-medical switch from originator infliximab to the biosimilar CT-P13 (Remsima) in all infliximab-treated IBD patients, with all new patients starting on CT-P13 thereafter. In April 2019, a second non-medical switch was undertaken from CT-P13 to another biosimilar, SB2 (Flixabi). This allowed us to study the effects on IBD disease activity and infliximab trough levels associated with switching from biosimilar CT-P13 to another biosimilar, SB2, and, importantly, to compare the impact of switching for the first time with patients switching for the second time to a third infliximab molecule.

2 | MATERIALS AND METHODS

2.1 | Study design

A single-centre, prospective observational cohort study was performed involving patients with IBD treated with infliximab biosimilar CT-P13 who underwent a non-medical switch to SB2. The non-medical switch was instituted as a cost-saving measure by the clinical team. As the department received a share of the savings in drug costs, which were then used to improve clinical care, there was a direct benefit to our IBD patients in undergoing the switch. All patients were informed of the planned switch both in writing and with posters around our infusion unit in the preceding weeks, and they were encouraged to raise concerns. No patients refused to switch.

Patients previously switched from infliximab originator CT-P13, and then switching to SB2, were defined as undergoing their second switch. Conversely, those who had not previously been on originator infliximab but were now switching from CT-P13 to SB2 were undergoing their first switch. Clinical and biochemical data including C-reactive protein (CRP) and clinical disease activity indices were collected prospectively at each infusion as part of routine clinical care. To assess disease activity, we collected Harvey-Bradshaw Index (HBI) for CD and Simple Clinical Colitis Activity Index (SCCAI) for UC with a score $\geq$ 5 defining active disease for both.\textsuperscript{19-21} Infliximab trough levels within 6 months of switch in patients on stable doses were collected and were repeated at the time of the third or fourth infusion of SB2 and again at 1 year. Loss of response of luminal disease (both CD and UC) was defined as the need for steroids, infliximab dose escalation or dose interval reduction, switch to another

Conclusions: Switching from one infliximab biosimilar to another had no adverse impact on infliximab trough levels, and clinical and biochemical disease activity, regardless of whether switching for the first or second time.
biologic, IBD-related hospitalisation or need for IBD-related luminal surgery. For perianal fistulating disease, loss of response was defined as infliximab dose escalation or dose interval reduction, switch to another biologic or IBD-related hospitalisation. Perianal surgery was only considered loss of response if it was non-elective or accompanied by change in biologic dose or interval or by switching to another biologic.

2.2 | Study population

We included adult IBD patients on stable dosing of CT-P13, defined as at least two infusions at the same dose and interval prior to the switch. Those who discontinued infliximab during the first 4 months of follow-up due to nondisease-related factors, such as moving to another hospital, were excluded. In addition, patients in whom the decision to discontinue or adjust treatment was based on investigations performed prior to the switch but in whom the decision to discontinue was not taken until after the switch had occurred were also excluded. As the data collected were part of routine clinical care, the study was considered a review of clinical practice and ethical approval was not required according to the guidelines of the UK Health Research Authority.22

2.3 | Infliximab and antiinfliximab antibody assays

Infliximab trough levels and antidrug antibodies (drug-sensitive assay) were performed using the LISA TRACKER assay (Theradiag) automated on the Dynex DS2 enzyme-linked immunosorbent assay (ELISA) processing system. Due to a change in the manufacturing process of the infliximab drug level assay, an assay comparison using a Passing–Bablok regression analysis was conducted on an independent cohort (n = 90) to establish comparability (Figure S1). Using the Passing–Bablok fit (new assay = 1.178 × original assay + 0.05), the correction was applied to values from samples analysed using the original assay. Levels <3 µg/mL were considered subtherapeutic.

2.4 | Statistical analysis

Descriptive statistics were used to illustrate patient disease, and drug and demographic characteristics. Fisher’s exact and chi-squared tests were used for comparing categorical variables, as appropriate. Independent t test and Mann–Whitney U test were used to compare independent normally and non-normally distributed data, respectively. With regard to assessing preswitch and postswitch continuous variables, the parametric paired samples t test or non-parametric Wilcoxon signed–rank test was used, whereas McNemar’s test was used for assessing for statistical difference between binary paired categorical variables. Given there was a statistically significant rise in infliximab level early after switch compared with before switch, regression analyses were performed to assess for factors associated with change in infliximab level.

Kaplan–Meier curves were generated for drug survival analyses, with the log-rank test used to compare survival between groups and Cox regression analysis performed for assessing the effect of covariates. Patients without loss of response but lost to follow-up within the year were censored at the time of last clinical assessment.

Factors with P value < 0.2 on univariable analyses or biologic plausibility were entered into multivariable analyses. As this was an observational cohort study, a power calculation was not performed. In analysing infliximab trough level, and clinical and biochemical outcomes at 1 year, patients who had infliximab dose adjustments during follow-up were excluded to remove the effect of dose alteration. Given some data were missing at 1 year, percentages presented and statistical analyses performed were on available data only, with denominators listed; P < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS v.23 (IBM Corporation).

3 | RESULTS

3.1 | Patient characteristics

Two hundred twenty-two patients underwent switching from CT-P13 to SB2 between April and June 2019: 186 patients met inclusion criteria, of whom 99 (53%) were undergoing their second switch (Table 1). Reasons for excluding 36 patients are outlined in Figure 1 and were predominantly due to unstable dosing before switch or change in dosing during the switch period based on preswitch disease activity or infliximab trough levels.

There was a higher proportion of first-switch patients with UC (35.6% vs 4%, P < 0.001); only four patients with UC were switching for the second time. This difference is likely due to the more recent UK national funding of infliximab in UC (2015) compared with CD (2010). Intuitively, second-switch patients had a longer median preswitch time since starting infliximab compared with first-switch patients (25 [interquartile range, IQR 16–44] vs 76 [IQR 23–197] months, P < 0.001). First-switch patients had higher median pre-switch infliximab trough levels (5.7 vs 4.3 µg/mL, P = 0.01), with a greater proportion of patients with levels >7 µg/mL.

3.2 | The early effect of switching on infliximab trough levels and disease activity

The median follow-up time at the early time point was 16 (IQR 16–19) weeks for both groups. Considering all patients, median infliximab trough levels were higher after switch compared with before switch (5.5 vs 4.9 µg/mL, P = 0.007) (Table 2). A similar trend in infliximab trough levels was observed when cases were stratified by switch group; median infliximab level rose among first-switch (5.7 vs 6.6 µg/mL, P = 0.05) and second-switch (4.3 vs 4.9 µg/mL, P = 0.07)
patients, although these changes did not achieve statistical significance (Figure 2). When stratified by infliximab trough level subgroups, there was no statistically significant change in distribution after switch (P = 0.10, Figure 3A). Two patients developed antidrug antibodies after switch, both switching for the first time and having had undetectable or very low (1.0 µg/mL) infliximab trough levels before switch.
There were no baseline demographic factors associated with early change in infliximab trough level after switch on univariable and multivariable linear regression (Table S1) nor was there any difference in the median number of days between infusions prior to the preswitch level and the early postswitch level (56 [IQR 56-59] days vs 56 [IQR 56-58] days, \( P = 0.23 \)). Preswitch infliximab trough

### TABLE 2 Infliximab trough levels and disease activity indices before switch, early after switch and at 1 year

| Patient group | Before switch | Early after switch | \( P \) value (before vs early) | 1 y after switch\(^a\) | \( P \) value (before vs 1 y) |
|---------------|----------------|-------------------|--------------------------------|----------------------|-----------------------------|
| **Infliximab trough level (\( \mu g/\text{mL} \), median [IQR])** | | | | | |
| All patients  | 4.9 (3.5-7.0)  | 5.5 (3.8-7.7)  | 0.007  | 5.3 (3.9-6.5)  | 0.08 |
| First switch | 5.7 (3.5-8.3)  | 6.6 (4.2-8.6)  | 0.05   | 5.7 (4.1-8.2)  | 0.37 |
| Second switch | 4.3 (3.2-6.2)  | 4.9 (3.5-7.0)  | 0.07   | 4.7 (3.5-6.1)  | 0.06 |
| **Positive antiinfliximab antibodies, cases (n)** | | | | | |
| All patients  | 0  | 2  | 0  | 0  |
| First switch | 0  | 2  | 0  | 0  |
| Second switch | 0  | 0  | 0  | 0  |
| **CRP (mg/L), median [IQR]** | | | | | |
| All patients  | 1.0 (0.5-3.0)  | 1.0 (0.5-3.0)  | 0.43   | 0.5 (0.5-2.0)  | 0.009 |
| First switch | 1.0 (0.5-3.0)  | 0.5 (0.5-2.0)  | 0.65   | 0.5 (0.5-1.0)  | 0.06 |
| Second switch | 2.0 (0.5-3.0)  | 2.0 (0.5-3.0)  | 0.32   | 0.5 (0.5-2.0)  | 0.06 |
| **CRP \( \geq 5 \text{mg/L}, n (\%) \)** | | | | | |
| All patients  | 28 (15.1)  | 23 (12.4)  | 0.41  | 17 (12.2)  | 0.47 |
| First switch | 15 (17.2)  | 11 (12.6)  | 0.34  | 7 (11.1)  | 0.30 |
| Second switch | 13 (13.1)  | 12 (12.1)  | 1.0   | 10 (13.2)  | 1.0 |
| **Clinically active disease (HBI or SCCAI \( \geq 5 \), n (\%)** | | | | | |
| All patients  | 17 (9.1)  | 15 (8.1)  | 0.82  | 7 (5.0)  | 0.73 |
| First switch | 9 (10.3)  | 4 (4.6)  | 0.06  | 6 (9.5)  | 1.0 |
| Second switch | 8 (8.1)  | 11 (11.1)  | 0.61  | 1 (1.3)  | 0.25 |
| **HBI, median [IQR]** | | | | | |
| All patients  | 0 (0-2.0)  | 0 (0-2.0)  | 0.87  | 0 (0-1.0)  | 0.002 |
| First switch | 0 (0-1.5)  | 0 (0-1)  | 0.85  | 0 (0-1.0)  | 0.18 |
| Second switch | 0 (0-2.0)  | 0 (0-2.0)  | 0.75  | 0 (0-1.0)  | 0.003 |
| **SCCAI, median [IQR]** | | | | | |
| All patients  | 0 (0-1.3)  | 0.5 (0-2.0)  | 0.87  | 0 (0-2.5)  | 0.24 |
| First switch | 0.5 (0-2.25)  | 0 (0-2.0)  | 0.20  | 0 (0-2.3)  | 0.44 |
| Second switch | 0 (0-0.75)  | 4 (0.5-8.5)  | 0.19  | 2 (0-3.0)  | 0.18 |

Abbreviations: CD, Crohn’s disease; CRP, C-reactive protein; HBI, Harvey–Bradshaw Index; IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.

\(^a\)Patients who were no longer on infliximab or who had infliximab dose or interval changes were excluded from 1-year analysis. At 1 year, infliximab trough levels were available for 118 patients (n = 55, first switch), CRP available for 139 patients (n = 63, first switch) and clinical scores available for 114 CD patients (n = 41, first switch) and 25 UC patients (n = 22, first switch).
level was associated with change in trough level after switch on univariable and multivariable analysis, such that lower preswitch trough levels were associated with a rise in infliximab level (standardised β coefficient −0.36, 95% confidence interval [CI] −0.51 to −0.22, P < 0.001).

With regard to disease control, there was no significant change in CRP or disease activity scores before vs early after switch, regardless of whether switching for the first or second time (Table 2). The proportion of cases in remission (HBI or SCCAI <5) did not change significantly (91% vs 92%, P = 0.75, Figure 3B). Nine patients (seven CD), all switching for the second time, developed clinically active disease (HBI or SCCAI ≥5) after switch with no significant change in infliximab trough levels. Only one of these cases developed a mildly elevated CRP (6 mg/L). Eleven patients (seven CD and six second switch) with clinically active disease at baseline entered clinical remission after switch.

3.3 | The effect of switching on drug levels, disease activity and immunogenicity at 1 year

One hundred seventy-eight (96%) patients had 1-year follow-up available, of whom 162 (91%) remained on infliximab (Figure S2). Loss of response was observed in 28 (16%) patients; 18 required dose escalation (n = 8, first switch), 6 ceased infliximab due to active disease (n = 2, first switch), whereas 4 met criteria for loss of response due to requiring hospitalisation (n = 2), surgery (n = 1) or steroids (n = 1) but continued infliximab treatment. Fourteen patients (n = 10, first switch) were either able to dose de-escalate (n = 5) or discontinue infliximab due to remission (n = 9). One patient ceased infliximab due to significant infection (second switch). Median infliximab trough levels were similar at 1 year compared with before switch (Table 2 and Figure 2). No cases had detectable antiinfliximab antibodies at 1 year.

There was no significant difference in time to loss of response between patients switching for the first or second time (P = 0.69, Figure 4). Higher preswitch infliximab level was associated with greater time to loss of response on univariable and multivariable Cox regression analysis (hazard ratio 0.79, 95% CI 0.66-0.94, P = 0.007), whereas greater time on infliximab before switch appeared to be associated with marginally greater time to loss of response on multivariable analysis but did not achieve statistical significance (hazard ratio 0.98, 95% CI 0.97-1.00, P = 0.05). No other variable, in particular first or second switch, was associated with loss of response (Table 3).

With respect to objective markers of disease activity at 1 year compared with before switch in those with stable infliximab dosing, there was no clinically significant change in CRP or disease activity scores (Table 2). Further, a similar proportion of patients had clinical disease activity (HBI or SCCAI ≥5.5.0% vs 9.1%, P = 0.16, Figure 3B) or biochemical activity (CRP ≥5 mg/L, 12.2% vs 15.1%, P = 0.47) at 1 year compared with before switch.

4 | DISCUSSION

This observational infliximab biosimilar switch study adds weight to the biosimilarity of CT-P13 and SB2 with respect to infliximab trough levels and disease control in patients with IBD and provides new insight into the clinical and pharmacokinetic acceptability of multiple biosimilar switches. There were two main findings. First, there was no adverse effect of switching biosimilar on infliximab trough levels or disease activity. Second, we have shown that whether patients were switching for the first or second time, the latter group predominantly being patients with CD, there was no significant difference in infliximab trough levels or disease activity either soon after switching or after a year. In addition, there was no significant difference in time to loss of response using clinically relevant definitions between...
the two groups. This raises the question of whether multiple anti-TNF switches might be plausible in IBD.

The reduced price of biosimilars offers significant opportunities in an area of spiralling healthcare expenditure. Economic modelling has predicted large savings through introduction of biosimilars. In addition to benefiting health systems generally, these cost savings may benefit patients directly by increasing or enabling earlier access to biologic therapies or by enabling dose intensification. The possibility of multiple switches opens up the potential for further cost savings through increasing competition.

Concerns surrounding the use of biosimilars stem from their molecular complexity despite the rigorous regulatory processes necessary to achieve authorisation. Biologicals are more complex and larger in size than non-biologic medicines, and their derivation from living cell lines subjects them to potential variability in their structural characteristics. In part because of potential inconsistencies associated with

FIGURE 3 Infliximab trough level subgroups (<3, 3-7 and ≥7 µg/mL) (A) and clinical disease activity (B), across time points. Active disease was defined as Harvey-Bradshaw Index or Simple Clinical Colitis Activity Index ≥5.
reproducing intricate manufacturing processes, replicated products are considered to be biosimilar and not bioidentical.24 Accordingly, the extrapolation of efficacy data across the originator’s indications based on clinical equivalence in a single disease has created controversy.8,9,11,24 Although acceptance of this approach has grown,9,11,12 disease-specific data are helpful and reassuring to clinicians and patients alike.

Because the PLANETRA and PLANETAS studies showed similar efficacy and safety between CT-P13 and originator infliximab in

**TABLE 3** Cox regression analysis of factors associated with time to loss of response

| Covariate                          | Univariable |                  | Multivariable |                  |
|------------------------------------|-------------|-----------------|---------------|-----------------|
|                                    | Hazard ratio (95% CI) | P              | Hazard ratio (95% CI) | P              |
| Female                             | 0.85 (0.40-1.82)     | 0.68           | 0.86 (0.41-1.89)     | 0.24           |
| Weight (kg)                        | 0.99 (0.96-1.02)     | 0.38           | 0.91 (0.38-2.18)     | 0.83           |
| Disease classification             | 0.57 (0.25-1.29)     | 0.17           | 0.65 (0.25-1.71)     | 0.38           |
| Perianal disease                   | 0.92 (0.38-2.22)     | 0.86           | 0.62 (0.25-1.56)     | 0.31           |
| Upper gastrointestinal disease     | 1.51 (0.44-5.15)     | 0.51           | 1.38 (0.08-1.89)     | 0.24           |
| Complicated Crohn’s disease        | 0.91 (0.38-2.18)     | 0.83           | 0.37 (0.12-1.15)     | 0.09           |
| Ileal or ileocolonic Crohn’s disease | 0.62 (0.25-1.56)    | 0.31           |                  |                |
| Extensive ulcerative colitis       | 0.38 (0.08-1.89)     | 0.24           |                  |                |
| Second switch                      | 0.86 (0.41-1.82)     | 0.69           | 0.37 (0.12-1.15)     | 0.09           |
| Baseline concomitant IM            | 1.51 (0.66-3.4)      | 0.33           |                  |                |
| Age at diagnosis                   | 1.02 (0.99-1.05)     | 0.08           | 1.01 (0.97-1.06)     | 0.61           |
| Age at induction                   | 1.02 (0.99-1.05)     | 0.11           | 0.99 (0.95-1.04)     | 0.84           |
| Time on infliximab before switch   | 0.99 (0.98-1.00)     | 0.11           | 0.98 (0.97-1.00)     | 0.05           |
| CRP at baseline                    | 1.01 (0.98-1.03)     | 0.58           |                  |                |
| Preswitch infliximab level         | 0.76 (0.64-0.91)     | 0.002          | 0.79 (0.66-0.94)     | 0.007          |
| Previous biologics                 | 0.98 (0.31-3.08)     | 0.97           |                  |                |

Note: Complicated Crohn’s disease was defined as penetrating or stricturing disease. Abbreviations: CI, confidence interval; CRP, C-reactive protein; IM, immunomodulator.
rheumatoid arthritis and ankylosing spondylitis, respectively, multiple real-world studies have occurred in IBD showing similar response rates and safety upon switching to or inducing with biosimilar CT-P13; these studies have been reviewed elsewhere. A Phase III double-blind study in biologic naïve CD patients randomised patients 1:1:1 to CT-P13 or Remicade induction, with continuation of induction drug or switch to the alternate drug at Week 30. Response rates were similar at the primary endpoint of Week 6 (77% vs 81%; difference of −4.9% [95% CI −16.9 to 7.3]) and Week 30 (85% vs 82%; difference of 1.3% [−10.3 to 12.9]), and although the study was not powered to detect statistical differences beyond Week 30, efficacy, safety and infliximab trough levels remained similar among the groups at Week 54.

In patients already established on originator infliximab, the pivotal NOR-SWITCH study demonstrated that switching from infliximab originator to CT-P13 was noninferior in terms of safety, efficacy and pharmacokinetics to continuing on the originator across multiple diseases (including 155 patients with CD and 93 with UC). Although not powered to show noninferiority in specific diseases, the CI was close to, but did not cross, the prespecified 15% noninferiority margin in CD, favouring originator (risk difference −14.3%, 95% CI −29.3 to 0.7). The Phase IV SIMILAR trial (NCT02452151) is currently underway to address this issue specifically in IBD.

However, very limited data are available with respect to switching between biosimilars in IBD with either long-term outcomes or drug levels lacking. We have shown that biosimilar-to-biosimilar switching does not have a negative influence in terms of infliximab trough levels and disease activity. The rate of loss of response at 1 year (16%) using a clinically relevant definition, including patients with low drug levels requiring dose escalation regardless of disease activity, was similar to that seen in previously reported cohorts of patients on long-term infliximab. In addition, there was no clinically significant change in clinical disease scores or CRP. Infliximab trough levels were not different at 1 year, and although a statistically significant rise early after switch (4.9 vs 5.5 \( \mu \text{g/mL} \), \( P = 0.007 \)) was detected, this small difference is unlikely to be of clinical significance and was no longer present after a year. Given that preswitch infliximab level was the only factor associated with change in infliximab level after switch on regression analyses, the change may be explained by regression towards the mean. Alternatively, the 12% rise observed may be related to assay or equipment-associated variability, as the established measurement of uncertainty, a quantitative indication of the quality of the result, with the ELISA platform used within our laboratory is <15%.

There are very limited data with respect to multiple switches of biologics. In a prospective real-world observational study of 174 IBD patients ‘reverse switching’ from CT-P13 to the originator Remicade, a small proportion (n = 14, 8%) had prior exposure to Remicade; no significant difference in clinical or infliximab trough level outcomes was seen by 24 weeks, regardless of prior exposure. A recent abstract reported equivalent safety and efficacy data to Week 48 between 52 double-switched IBD patients (originator to CT-P13 to SB2) and 66 single-switched controls (originator to CT-P13). Likewise, similar safety and efficacy data were reported at 1 year between 24 double-switched patients (originator to CT-P13 to SB2) and a heterogeneous group commencing SB2 who were either naïve to anti-TNF, infliximab, or being switched from CT-P13 or originator. However, no infliximab trough level data were available in either of the two aforementioned studies. Reassuringly, in a study of patients with an array of chronic inflammatory disorders on infliximab switched to a biosimilar once (originator to CT-P13) or twice (originator to CT-P13 to SB2), the number of biosimilars received was not associated with immunogenicity.

We present a large cohort with both clinical and infliximab trough level data; 99 patients were switching for the second time, having previously switched from originator infliximab to CT-P13, and 87 were switching for the first time. Importantly, there was no significant difference between first- and second-switch patients with regard to time to loss of response, disease activity scores, CRP or infliximab trough levels both early and 1 year after switching. Intuitively, second-switch patients had a longer median time on infliximab before switch compared with first-switch patients (76 vs 25 months, \( P < 0.001 \)). Although the nonstatistically significant lower rate in immunomodulator use among second-switch patients may relate to thiopurine withdrawal after prolonged concomitant use, multivariable analysis did not identify immunomodulator use as a factor associated with clinical outcomes or infliximab trough levels.

We acknowledge a number of limitations of this study. The lack of a nonswitching control group might be seen as a limitation, although there are many studies that already compare switching with nonswitching cohorts; by comparison, we wished to compare cohorts switching for the first and second times. The manufacturer’s change in the infliximab assay that occurred during the study period had the potential to affect measurement of drug levels over the course of the study. However, this was mitigated by applying a conversion factor established from an independent cohort, and as a result, the version of the assay had no effect on change in infliximab level on regression analysis (standardised \( \beta \) coefficient 0.01, 95% CI −0.13 to 0.16, \( P = 0.86 \)). Furthermore, studies have shown that measuring drug levels of different biosimilars as well as measuring antinfliximab antibodies is feasible across different assays.

An area that may influence the generalisability of our findings relates to the small number of UC patients in the second-switch group. This likely occurred as a result of the more recent reimbursement of infliximab in UC compared with CD in the United Kingdom and potentially limits the strength of conclusions that can be drawn from first- and second-switch comparisons in UC patients. However, there is limited reason to expect a second switch in UC to behave differently to CD, and disease type had no impact on outcomes on multivariate analyses. In addition, the use of a drug-sensitive assay would have limited our ability to detect the formation of new antinfliximab antibodies following switching. However, the clinical relevance of antidrug antibodies in the presence of detectable drug is debated. For example, in an analysis of the TAXIT study, there was no significant difference in clinical, biochemical and endoscopic...
remission rates in patients requiring dose optimisation based on drug levels whether low-level antiinfliximab antibodies were detectable or low infliximab drug levels, which is an indication for treatment optimisation in our practice and hence would have been captured in our survival analysis. Finally, neither routine endoscopy nor collection of faecal calprotectin was performed. Although this is an inherent weakness of ‘real-world’ data collection, it is mitigated by the consistent collection of clinical disease activity scores, the relevant definition of loss of response and, importantly, the infliximab trough level data.

In conclusion, in this 1-year observational study of IBD patients established on infliximab therapy, switching from one infliximab biosimilar to another had no adverse impact on infliximab trough levels and disease activity. Furthermore, findings were similar among patients switching for the first or second time, supporting the possibility of multiple switches. There remains, however, a need to agree on the quality of evidence required to adopt this practice widely, as the performance of large-scale, randomised controlled trials of multiple switching for each individual biosimilar is probably unrealistic.

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AUTHORSHIP

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Author contributions: The study was conceived by R. P. L., R. O., Z. A., M. A. S. and P. M. I., with data collection performed by R. P. L., R. O., E. S., S. S., G. C., S. H., Z. A., S. R., S. H. A., J. M., J. D. S. and S. M. The data were analysed and manuscript drafted by R. P. L., Z. A., M. S. and P. M. I., and all authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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**SUPPORTING INFORMATION**

Additional supporting information will be found online in the Supporting Information section.

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