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Ratnakumaran, R, To, N, Gracie, DJ orcid.org/0000-0001-9616-981X et al. (8 more authors) (2018) Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scandinavian Journal of Gastroenterology, 53 (6). pp. 700-707. ISSN 0036-5521

https://doi.org/10.1080/00365521.2018.1464203

Accepted for publication 2nd April 2018

Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in Inflammatory Bowel Disease (IBD): A large single-centre experience

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ABSTRACT

Objectives:

Recently, the infliximab biosimilar (CT-P13) received market authorisation for inflammatory bowel disease (IBD), allowing cost benefits when switching to CT-P13. We aim to assess the efficacy and safety of switching from originator infliximab to CT-P13 for new and existing patients.

Material and Methods:

Treatment response, remission, primary and secondary loss of response rates, and adverse events in patients who initiated infliximab originator in the 12 months pre-switch (n=53) were compared with the patients who initiated CT-P13 in the 12 months post-switch (n=69). Sustained responses were compared for existing infliximab originator patients
who switched to CT-P13 (n=191) and those who continued with the originator (n=19).

Results:

There was no difference in remission (58.1% vs. 47.4%, P = 0.37), response (12.6% vs. 10.5%, P = 0.80), secondary loss of response (24.6% vs. 42.1%, P = 0.10), or adverse events (4.7% v 0% P = 1.0) between those who switched to CT-P13 and those who continued infliximab originator. There was no difference in remission (42.0% vs. 26.4%, P = 0.074), response (21.7% vs. 22.6%, P = 0.91), primary non-response (5.8% vs. 15.1%, P = 0.09), secondary loss of

response (21.7% vs. 22.6%, P = 0.91), or adverse events (8.7% vs. 11.3%, P = 0.63) in those who initiated CT-P13 compared with infliximab originator.

Conclusions:
There was no difference in the efficacy and safety of infliximab originator and CT-P13 during the first 12 months after switching.

Abbreviations:

IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn's disease
IBD-U	inflammatory bowel disease-unclassified
TNF	tumour necrosis factor
HBI	Harvey-Bradshaw index

Keywords: Biosimilar
Infliximab
CT-P13
Inflammatory Bowel Disease
Biologics

Funding: None

Introduction

Inflammatory bowel disease (IBD) is a relapsing and remitting inflammatory disorder of the gastrointestinal tract, with Crohn's disease (CD) and ulcerative colitis (UC) constituting the two main types [1]. The aetiology of these disorders is multifactorial and involves an interaction between genetic, environmental and immune regulatory factors in the gastrointestinal mucosa [2,3]. Over the last 20 years, targeted biological therapy against these immune regulators, such as tumour necrosis factor-alpha (TNF-α), has evolved rapidly, revolutionising the medical management of IBD [4-6]. Infliximab is a monoclonal IgG1 antibody against TNF-α, and has been licensed for the treatment of both CD and UC [7,8]. However, biological agents such as infliximab are more expensive than traditional treatments, and have substantial cost implications for service providers [9].

Recently, a biosimilar agent has been developed for infliximab, known as CT-P13 (Remsima®, Celltrion, Republic of Korea and Inflectra®, Hospira, UK). CT-P13 has shown to be very similar to Infliximab originator (Remicade®, Centocor Ortho Biotech Inc, Pennsylvania, USA) in terms of physiochemical properties, pharmacokinetics, immunogenicity, safety, and efficacy across some, but not all, indications [10-13]. The use of the biosimilar infliximab CT-P13 (Remsima® and Infectra®) was approved by the European Medicine Agency in 2013, and the Food and Drug Administration in 2016 [11][25]. The major advantage of the use of CT-P13 is its significant cost-saving implications when switching from the infliximab originator with an estimated annual saving of £5400 per patient, based on a 70kg patient receiving 5mg/kg 8-weekly.

Despite a lack of randomised controlled trials (RCT) of CT-P13 in patients with IBD, several observational studies have shown this biosimilar agent to be both effective and safe [14-21]. More recently, a phase 4 randomised double blind, non-inferiority trial, the NORSWITCH study, has been completed [22]. This demonstrated no difference in clinical efficacy or safety between CT-P13 and

infliximab originator across several indications, including IBD, psoriasis, axial spondyloarthropathies and rheumatoid arthritis [22].

In our centre for IBD, over 200 patients receive infliximab for CD or UC. Due to prospective collection of data of each patient on commencement of infliximab, and continued data collection thereafter, we are able to accurately assess the efficacy, tolerability, and safety of infliximab therapy in our patient cohort. We present our experience of switching patients from the infliximab originator to CT-P13, and initiating patients on CT-P13. Our a priori hypothesis was that there would be no difference in efficacy or safety between the two.

Material and Methods

Participants and Setting

The IBD outpatient clinic in Leeds Teaching Hospitals Trust, Leeds, United Kingdom has been treating patients with infliximab since the year 2000. This is a large teaching hospital in a city in the North of England, which serves a population of approximately 800,000. The majority of patients receive infliximab as scheduled maintenance therapy, defined as a three-dose infliximab induction regimen of 5mg/kg at 0, 2, and 6 weeks, followed by regular 8-weekly infusions thereafter. Patients not on concomitant immunomodulators are routinely given intravenous hydrocortisone prior to each infusion. An IBD nurse specialist at the Leeds Immune Mediated Inflammatory Disease Unit administers the infusions. The patients then attend an outpatient clinic where a gastroenterologist assesses the treatment response, and a decision is made whether or not to continue the infliximab based on symptom response, inflammatory markers and, in some cases, disease activity scores.

This observational study included patients who were receiving infliximab originator therapy (Remicade®) for CD or UC in our centre. The infliximab biosimilar (CT-P13) was introduced in our centre on 1st February 2016. Prior to switching patients to CT-P13, we explained the proposed switch to our IBD

patient group, and each patient provided written informed consent. Only a minority of patients wished because of personal choice to continue with the originator. We aimed to assess whether it was effective and safe to switch patients on stable infliximab originator treatment for inflammatory bowel disease to CT-P13, and also to examine whether CT-P13 was as effective and safe as infliximab originator, to use in patients who were newly commenced on infliximab therapy.

Data Collection

Demographic data collected included age, sex, indication (luminal CD, fistulising CD, UC, IBD-U), disease duration, duration of infliximab therapy, concomitant immunomodulators, and C-reactive protein (CRP) levels. HBI or partial Mayo scores were recorded prospectively, before induction therapy commenced. On commencement of infliximab therapy, data concerning the type of induction regimen used, patients' symptom response, CRP levels, need for either a subsequent dose escalation of infliximab to 10mg/kg, or a reduction in interval of dosing to 6-weekly infusions to maintain or recapture response, addition of glucocorticosteroids, requirement for subsequent surgery, switching to an alternative biological therapy, or any adverse events, were recorded.

Primary End-Points

In order to assess the effectiveness and safety of switching patients who had responded to, or were in remission with, infliximab originator therapy for IBD to CT-P13, we collected data as above for all individuals who provided informed consent to switch to CT-P13, as well as those who elected to continue receiving the infliximab originator. Treatment remission and response rates, secondary loss of response rates, and adverse events were compared between existing infliximab originator patients who switched to CT-P13 on 1st February 2016, and those who continued with the originator.

In order to assess the effectiveness and safety of CT-P13 in anti-TNF-α

naïve patients, we collected data for all patients who commenced infliximab originator for the first time in the 12 months prior to the switch date (1st of February 2015 to 31st of January 2016), and compared their outcomes with patients who commenced CT-P13 for the first time in the 12-month period after the switch (1st of February 2016 to 31st of January 2017). Endpoints of interest included treatment response and remission rates, primary and secondary loss of response rates, and adverse events in those patients who completed induction therapy with infliximab, in order to allow enough time to assess treatment response and remission.

Definition of Primary End-Points

Remission was defined when patients were asymptomatic, which was determined by the physician at their clinic visit, with a CRP <5mg/L, and who were no longer requiring glucocorticosteroid treatment. Remission for patients with fistulising CD was defined as complete closure of all draining fistulae. Response was defined as a symptomatic response when assessed at clinic by the physician, with an improving CRP, or HBI or partial Mayo score. In patients with fistulising CD, treatment response was defined as an improvement in drainage from fistulae, based on a physician's assessment. Primary non-responders to CT-P13 or infliximab originator were defined as patients who failed to achieve a response to the drug after 3 months of therapy. The drug was discontinued in all primary non-responders. Secondary non-responders to CT-P13 or infliximab originator were defined as patients who had initially responded to induction therapy, but who experienced a relapse of disease activity according to a physician's global assessment. This included the need for rescue therapy with glucocorticosteroids, an escalation in dose to 10mg/kg, a reduction in the dosing interval, a change to an alternative biological agent, or surgery. Adverse events were defined as intolerable side effects that led to discontinuation of the drug.

Serum Drug and Antibody assessment

Total anti-infliximab antibody levels and infliximab trough levels were measured prior to the switch to CT-P13, and at 3, 6, and 12 months post-switch. The free antibodies against infliximab and infliximab trough levels were determined using enzyme-linked immunosorbent assay. To test for presence of antibodies against infliximab, the serum free anti-infliximab antibodies are bound to the infliximab F $(ab)_2$ fragments coated on a plate. To test for infliximab drug levels in serum, the free infliximab from the sample are bound to specific monoclonal anti-infliximab antibody coated on a plate. In both tests a washing step was carried out, followed by incubation with peroxidase-labeled therapy antibody. This was followed by the addition of tramethylbenzidine (a substrate for perioxidase), and an acidic solution to terminate the reaction. This reaction causes a colour change, and the intensity of the colour is proportional to the amount of anti-infliximab antibodies and infliximab drug levels in both tests. [23,24] An infliximab drug level of <0.8mg/L was defined as unrecordable, <2.0mg/L was defined as low, a level between 2.0mg/L and 5.9mg/L was defined as therapeutic, while a level ≥6.0mg/L was supratherapeutic. Total anti-infliximab antibody levels were recorded as positive if >10 AU/mL, and antibody levels >50 AU/mL were considered clinically relevant. The ranges were determined after discussion with the clinical laboratory that analysed the samples.

Statistical Analyses

All continuous data were analysed using a mean with a standard deviation, and all ordinal data were averaged using a median with an inter-quartile range. All categorical data were measured as proportions, and compared between groups using the Pearson $\chi 2$ statistic, or Fisher's exact test where cell counts were small. P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc, Chicago, Illinois, USA).

Ethical Consideration

The study was conducted as a prospective clinical audit and relevant clinical audit authorisation was obtained. Due to the nature of audit, research ethics committee approval and informed consent were not required.

Results

Effect of Switching from infliximab originator to CT-P13 on Rates of Remission, Response, Secondary Loss of Response, and Adverse Events

In total, 210 patients were receiving maintenance infliximab originator therapy for IBD in our centre, prior to the switch date in February 2016. Of these, 191 (91.0%) patients consented to switch to CT-P13, and 19 (9.0%) continued on the originator. Of the 191 patients who switched to CT-P13, 87 (45.5%) were female, mean age was 42.7 years, and mean duration of infliximab therapy was 55 months. Overall, 129 (67.5%) of those who switched were receiving infliximab for luminal CD, 44 (23.0%) for fistulising CD, 14 (7.3%) for UC, and four (2.1%) for IBD-U. In the 19 patients who continued on infliximab originator 12 (63.2%) were female, mean age was 38.4 years, and mean duration of infliximab therapy was 53.9 months. Of these, 11 (57.9%) were receiving infliximab for luminal CD, four (21.1%) for fistulising CD, and four (21.1%) for UC. The two treatment groups were similar for all baseline demographic characteristics, although there were a greater proportion of patients with UC who continued on infliximab originator compared with those who switched to CT-P13 ($P = 0.04$) (Table 1).

[Table 1 near here]

Overall, 111 (58.1%) of 191 patients who switched to CT-P13 and nine (47.4%) of the 19 who continued the infliximab originator were still in remission 12 months post-switch (P = 0.37). Another 24 (12.6%) patients who switched to CT-P13 and two (10.5%) of those who continued the originator were judged to have a clinical response but did not achieve remission (P = 0.80). Of the 44 patients with fistulising CD switched to CT-P13 from the infliximab originator, 22 (50.0%) were in remission, 11 (25.0%) were deemed clinical responders, nine (20.5%) were deemed secondary non-responders, and two (4.5%) developed adverse reactions, 12 months post-switch.

Forty-seven (24.6%) patients who switched to CT-P13 and eight (42.1%) who continued on infliximab originator were deemed secondary non-responders (P = 0.10). Decisions and subsequent outcomes among those with a secondary loss of response after switching to CT-P13 or continuing with the originator are detailed in Figures 1 and 2 respectively. Finally, adverse events occurred in nine (4.7%) patients who switched to CT-P13, but in none of the patients who continued the infliximab originator (P = 1.0). Of the nine patients who developed an adverse event following the switched to CT-P13, four developed dermatitis, three developed an infusion reaction, one developed a cavitating lung lesion, and one patient developed a neurological syndrome of headache and loss of consciousness that recurred even after the patient was subsequently switched back to the originator. No significant change in mean CRP was observed among patients before and 3 months after the switch (7.0 ($\pm 7.3\ s.d$) vs. 6.5 ($\pm 5.4\ s.d$) respectively, P = 0.53). At 12 months following the switch to CT-P13, 146 (76.4%) patients maintained their response to infliximab, compared with twelve (63.2%) patients who continued on the infliximab originator (P = 0.20) (Figures 1 and 2).

[Figure 1 and Figure 2 near here]

Effect of infliximab originator and CT-P13 on Rates of Induction of Remission, Primary Loss of Response, and Adverse Events in Anti-TNF-α Naïve Patients

There were 69 patients who newly commenced CT-P13 in the subsequent 12 months, of whom 34 (49.3%) were female and the mean age was 36.5 years. Of these, 22 (31.9%) patients had luminal CD, nine (13.0%) had fistulising CD, 35 (50.7%) had UC, and three (4.3%) had IBD-U. This compared with 53 anti-TNF-α naïve patients who newly commenced infliximab originator in the 12 months prior to the switch to CT-P13. Of these, 29 (54.7%) were female and the mean age was 38.2 years. There were 26 (49.1%) patients with luminal CD, 13 with fistulising CD (24.5%), 13 (24.5%) with UC, and one (1.9%) with IBD-U. The two treatment groups differed in baseline disease characteristics, with a greater proportion of UC patients in the CT-P13 cohort (50.7% vs. 24.5%, P = 0.003). The CT-P13 treatment group also had a higher mean CRP (20.2 vs. 10.6, P = 0.008), but a lower median partial Mayo score (5 vs. 11, P = 0.007) (Table 2).

[Table 2 near here]

Remission occurred in 29 (42.0%) patients who commenced CT-P13 and 14 (26.4%) patients who commenced infliximab originator (P = 0.07). Treatment response occurred in a further 15 (21.7%) patients who commenced CT-P13 and 12 (22.6%) patients who commenced infliximab originator (P = 0.91). Primary non-response occurred in four (5.8%) who commenced CT-P13 and eight (15.1%) patients who commenced infliximab originator (P = 0.09). Secondary loss of response occurred in 15 (21.7%) patients who commenced CT-P13 and 12 (22.6%) patients who commenced infliximab originator (P = 0.91). Of the nine patients with fistulising CD who newly commenced CT-P13, five (55.6%) achieved remission, three (33.3%) were deemed clinical responders, and one (1.1%) developed an adverse reaction. Decisions and subsequent outcomes among those with a secondary loss of response after newly commencing

infliximab originator or CT-P13 are detailed in Figures 3 and 4 respectively. One (2%) patient stopped the infliximab originator after changing their decision on initiating infliximab therapy. Finally, adverse events occurred in six (8.7%) treated with CT-P13 and six (11.3%) patients treated with the originator (P = 0.95). In the six patients who had adverse events following initiation of CT-P13, five developed an infusion reaction and one patient developed a drug-induced rash. In the six patients who had adverse events following initiation of infliximab originator, four developed an infusion reaction, one developed severe joint pains, and one developed a blood abnormality. There was no difference in the rate of infusion reactions in those who initiated CT-P13 compared with those who infliximab originator, (five (7.2%) vs. four (7.5%), P = 0.95).

[Figure 3 and 4 near here]

Effect of Drug and Antibody Levels on Remission Rates

Drug and antibody levels were measured before the switch to CT-P13 in 129 patients. Ninety (69.8%) patients had supratherapeutic or therapeutic drug levels with no significant antibodies, and four (3.1%) patients had supratherapeutic or therapeutic drug levels with antibodies, prior to switching to CT-P13. Ten (7.8%) patients had low or unrecordable drug levels with clinically relevant antibody levels, and there were 25 (19.4%) patients with low or unrecordable drug levels, but no clinically relevant antibody levels. Patients with therapeutic drug levels and no clinically relevant antibody levels pre-switch were more likely to be in clinical remission 12 months after the switch, compared with patients with low or unrecordable drug levels and clinically relevant antibody levels (60 (66.7%) vs. 2 (20.0%), P = 0.004)). Table 3 demonstrates the relationship between infliximab drug and antibody levels prior to the switch to CT-P13, and treatment response 12 months post-switch.

[Table 3 near here]

Rates of loss of response or discontinuation of therapy at 12 months post-switch were significantly lower in those with therapeutic drug levels and no significant drug antibodies, compared with patients with low or undetectable drug levels and significant antibodies (18 (20.0%) of 90, compared with 7 (70.0%) of 10 (P <0.001), and 6 (6.7%) of 90 compared with 6 (60.0%) of 10 (P <0.001) respectively).

Discussion

This prospective observational study demonstrates the real-life clinical outcomes of switching patients from infliximab originator to CT-P13, and initiating patients on CT-P13, in a large IBD centre. Our study demonstrates that it is both effective and safe to switch patients to CT-P13 from infliximab originator, and to initiate CT-P13 in anti-TNF-α naïve patients. We also demonstrated that measuring drug and antibody levels before switching could be useful in predicting treatment response.

Our real-life clinical data show that there is no difference in remission, response, secondary loss of response, adverse events or changes in clinical laboratory parameters such as CRP after switching to CT-P13. Both groups had similar baseline characteristics, although more patients who continued the originator had UC. In the present cohort, drug related adverse events causing discontinuation of therapy were experienced in 4.7% of patients following the switch until 12 months. Our data also showed that there is no difference between remission, response, primary and secondary loss of response or adverse effects in anti-TNF-α naïve patients who newly commenced infliximab originator in the 12 months prior to the switch to CT-P13 compared to those who newly commenced CT-P13. We did observe differences in baseline characteristics

between infliximab new starters that are likely to be due to the date of commencement of infliximab originator and CT-P13. A higher proportion of patients who newly initiated CT-P13 had UC compared to those who initiated infliximab originator a year earlier. This is likely to be attributable to the increased use of infliximab in patients with UC in our centre, particularly after the United Kingdom National Institute of Health and Care Excellent (NICE) approved its use in moderate to severe UC in 2015 [27]. In anti-TNF-α naïve patients who initiated CT-P13, 8.7% of patients experienced drug related adverse events causing discontinuation over the 12 months, and infusion reactions occurred in 7.2% of patients. Our study findings have shown that the presence of low/undetectable drug levels and clinically relevant antibodies before the switch is associated with an increase likelihood of loss of response or discontinuation of the drug at 12 months. Patients who lost response were found to have lower infliximab trough levels and higher anti-infliximab antibody levels prior to the switch to CT-P13. This suggests that these patients may have gone on to lose response, regardless of the switch to CT-P13.

Strengths of this study include prospective data collection with the inclusion of patients who initiated or switched to CT-P13 from a large, predominantly secondary care population, meaning that these results are likely to be generalisable to the wider IBD population. A total of 191 patients were switched to CT-P13, making this to date one of the largest cohorts of patients with IBD switched to CT-P13 from the infliximab originator. In addition, we present complete demographic and disease related characteristics, which is a further strength. A limitation of this study, arising from its observational nature, was that patients were not randomised to the treatment groups, resulting in a large disparity between the patient numbers in each group. A further limitation is that we compared infliximab originator and CT-P13 new starters from two separate time periods, which may explain the differences in baseline characteristics of the groups. Despite the prospective data collection, we were unable to collect HBI or partial MAYO scores for all the patients during the follow-up period.

Our study findings after switching patients to CT-P13 mirrored those of the NORSWITCH study and other smaller observational studies [22]. In a retrospective multi-centre observational study from South Korea, 27 patients with CD and 9 patients with UC were switched to CT-P13. They found that 92.6% of CD patients and 66.7% of UC patients' maintained similar response compared with infliximab originator [16].

Similarly, a single-centre observational study in Spain found that after switching all patients from infliximab originator to CT-P13, response was maintained in 84% with CD and in 91.3% with UC [14]. A single-centre observational study in the Netherlands also matched our findings and demonstrated no difference in disease activity scores, CRP and faecal calprotectin after the switching to CT-P13 [21]. Our data on initiating CT-P13 in anti-TNF-α naïve patients were consistent with the randomised controlled trials comparing CT-P13 and the infliximab originator in rheumatoid arthritis and ankylosing spondylitis [12-13]. Our data on serum drug and antibodies levels are also in line with a meta-analysis published in 2013, which showed that the presence of anti-infliximab antibodies is associated with a higher risk of loss of clinical response to infliximab [26].

The data from this study is important, as it further validates and supports findings from other studies, that it is safe and effective to initiate and/or switch to CT-P13 from an infliximab originator in 12 months of follow up. In comparison to other published data, we have one of the largest cohorts of patients with IBD switched to CT-P13 from the originator and we provide longer-term follow-up data after initiating and/switching to CT-P13. We also demonstrate a novel observational study, which compares those who have initiated CT-P13 against those who have initiated the infliximab originator and comparing those who have switched to CT-P13 against those who have continued the originator, which are limited in the literature. Our study also shows the importance of measuring infliximab drug and antibody levels prior to switching to CT-P13, and its potential role in predicting loss of response after the switch. It can act as a tool for clinicians to decide whether it is appropriate to switch to a biosimilar, or to an

alternative biological agent altogether. The NORSWITCH study has demonstrated that immunogenicity did not differ between those who to switched CT-P13, or those who continued the infliximab originator as the infliximab drug and antibody levels were similar throughout the follow up period in both groups [22].

The majority of our IBD patients were very receptive to the switch to CT-P13. However, a small proportion of patients elected initially to continue with the infliximab originator product. These patients were concerned that a switch to a biosimilar would lead to an IBD flare. Despite their initial concerns, we noted that a number of these patients later switched to CT-P13 after seeing other patients in the Immune Mediated Inflammatory Disease Unit tolerating the biosimilar well, with few flares.

By switching to CT-P13 in 191 patients in our unit, we saved over £1million a year. There are significant cost saving benefits to service providers when switching to a biosimilar, which can facilitate efficient allocation of scarce financial resources. Due to the cost-benefits we believe that biosimilars should be used by healthcare services when approved by the FDA or EMA, and if there are studies to suggest the biosimilar agent has similar safety, efficacy and immunogenicity profiles to the originator product in a particular disease indication. Current evidence suggests that it is safe to switch CT-P13 from the infliximab originator for IBD, however the effects of interchanging from one biosimilar to another or even back to the originator is currently been studied.

Overall, CT-P13 is a cheaper, safe and effective alternative to infliximab originator. These data highlight that there is no difference in remission, response, loss of response or adverse events when initiating or switching to CT-P13 compared with initiating or continuing infliximab originator for IBD. Our findings are supported by randomised control trials and other post-marketing observational studies. Coupled with data from other studies showing no difference in immunogenicity after switching to CT-P13, our study supports initiating CT-P13 in IBD when indicated, and switching from infliximab originator to a biosimilar agent as a cost-effective treatment in IBD.

Acknowledgements: None

Declaration of interests: RR: none. NT: none. DJG: none. CPS has served on advisory boards and received speakers' fees from MSD. TC: none. NC: none. KL: none. LB: none. ACF has received speakers' fees from MSD. PJH has served on advisory boards and received speakers' fees from MSD.

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