Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial

*Anne S Strik, Wim van de Vrie, Joanne P J Bloemsaat-Minekus, Michael Nurmohamed, Peter J J Bossuyt, Alexander Bodelier, Theo Rispens, Yvonne J B van Megen, Geert R D'Haens, on behalf of the SECURE study group**

Summary

Background Biological treatment of chronic inflammatory diseases has improved patient outcomes but increased health-care costs. Switching patients from originator infliximab to a biosimilar can reduce costs, but prospective data about pharmacokinetics and potential immunogenicity are scarce. We aimed to show that infliximab serum concentrations with biosimilar CT-P13 are non-inferior to those with originator infliximab after switching from originator infliximab in patients with inflammatory bowel disease.

Methods SECURE was a prospective, open-label, interventional, non-inferiority, multicentre, phase 4 trial at 13 academic and non-academic sites in Belgium and the Netherlands. Eligible participants were aged 18 years or older, had ulcerative colitis or Crohn's disease, were in clinical remission, and were on continuous treatment with originator infliximab for more than 30 weeks. Patients were switched from originator infliximab to CT-P13 at a dose and infusion duration identical to those of originator infliximab (ie, ~5 mg/kg every 7–9 weeks). Patients were followed up for 16 weeks after switching, with serum concentrations of infliximab measured at baseline (before the first dose of CT-P13), 8 weeks, and 16 weeks. The primary endpoint was serum concentrations of infliximab 16 weeks after switching, assessed separately in patients with ulcerative colitis and those with Crohn's disease in the per-protocol population, which included all patients with available serum concentrations and without major protocol violations. A non-inferiority margin of 15% was set (the null hypothesis was that the geometric mean of the ratio of serum infliximab concentrations at 16 weeks to those at baseline was 85% or less). Safety analyses were done in the safety population, which included participants who received at least one dose of CT-P13 and attended at least one safety assessment after that dose. This trial is registered at www.ClinicalTrialsRegister.eu, number 2014-004904-31, and is completed.

Findings Between June 5, 2015, and April 6, 2016, 120 consecutive patients with inflammatory bowel disease were recruited: 59 with ulcerative colitis and 61 with Crohn's disease. 46 patients with ulcerative colitis and 42 patients with Crohn's disease comprised the per-protocol population. The geometric mean ratio of serum infliximab concentrations at week 16 (CT-P13) compared with those at baseline (originator) was 110·1% (90% CI 96·0–126·3) in patients with ulcerative colitis and 107·6% (97·4–118·8) in those with Crohn's disease. In both cases, the lower bound of the 90% CI was higher than the prespecified non-inferiority margin of 85%. Six serious adverse events were reported in six patients. Only one of these adverse events, a perianal abscess, was judged to be related to study treatment.

Interpretation Switching to CT-P13 is safe and well tolerated in patients with inflammatory bowel disease in remission. Future trials should assess switching to CT-P13 in patients with active disease.

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*Members listed at end of paper

Department of Gastroenterology (A S Strik MD, Prof G R D'Haens PhD) **and Landsteiner Laboratory** (T Rispens PhD), **Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Department of Gastroenterology, Albert Schweitzer Hospital, Dordrecht, Netherlands** (W van de Vrie PhD); **Mundipharma, Leusden, Netherlands** (J P J Bloemsaat-Minekus PhD, Y J B van Megen PhD); **Department of Rheumatology, Reade, Amsterdam, Netherlands** (Prof M Nurmohamed PhD); **Department of Gastroenterology, Imelda Hospital, Bonheiden, Belgium** (P J J Bossuyt PhD); **Department of Gastroenterology, Amphia Hospital, Breda, Netherlands** (A Bodelier PhD); **and Sanquin Research, Department of Immunopathology, Amsterdam, Netherlands** (T Rispens)

Correspondence to: Prof Geert R D'Haens, Department of Gastroenterology, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, Netherlands **g.dhaens@amc.uva.nl**

Introduction

After the European patent expiry date of originator infliximab (Remicade; Johnson & Johnson, New Brunswick, NJ, USA) in 2015, the biosimilar infliximab CT-P13 (Celltrion, Incheon, South Korea) was introduced. CT-P13 is produced in the same type of cell line as originator infliximab and has an identical aminoacid sequence.[1] Biosimilars are highly similar but not identical to originator biological drugs because of the structural complexity and manufacturing procedures, leading to potential differences in biochemical attributes. The most important reason to use biosimilars is to reduce health-care costs and thereby potentially increase access to biological treatment, even in countries with weak health-care systems.

The European Medicines Agency approved CT-P13 in 2013 for the treatment of autoimmune diseases, with the same indications as originator infliximab. This approval

Research in context

Evidence before this study

We searched PubMed with the terms "biosimilar", "infliximab", "CT-P13", "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "rheumatoid arthritis", "ankylosing spondylitis", and "switch" for randomised controlled trials and observational trials published in any language up to Dec 11, 2017. We also included unpublished conference abstracts. We identified both prospective studies and retrospective studies, but published work about switching from originator infliximab to biosimilar CT-P13 was scarce, although more evidence became available as we wrote this Article. The use of biosimilars can reduce health-care costs. In most countries, patients with inflammatory bowel disease who are starting infliximab treatment receive the biosimilar CT-P13. Increasing evidence shows that switching patients from infliximab to the biosimilar is effective and safe, but little evidence is available.

Added value of this study

In our trial, serum concentrations of infliximab 16 weeks after switching to CT-P13 were non-inferior to those with originator infliximab in patients with stable disease on maintenance therapy. Likewise, no difference in immunogenicity, as measured by concentrations of anti-drug antibodies, was noted before and after switching. Switching was safe and well tolerated.

Implications of all the available evidence

Switching patients with stable inflammatory bowel disease to CT-P13 is safe and well tolerated. However, our results cannot be extrapolated to patients with active disease.

was based on trials[2,3] done in patients with ankylosing spondylitis and rheumatoid arthritis, in which CT-P13 was equivalent to originator infliximab in terms of pharmacokinetic profile, efficacy, and safety. No biosimilar studies were done in patients with inflammatory bowel disease before the European Medicines Agency approved CT-P13 for this disease, and thus uptake of the biosimilar by gastroenterologists was initially slow. Furthermore, no clear guidance about switching patients taking originator infliximab who are in remission was offered by scientific societies such as the European Crohn's and Colitis Organisation, and some patients' associations even issued statements of caution.[4]

NOR-SWITCH, a large government-sponsored Norwegian trial,[5] was the first randomised controlled study of switching done in patients with inflammatory bowel disease (it also included patients with psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis). Patients were randomly assigned to either continuing originator inflixmab treatment or to switch to CT-P13 for 52 weeks. No differences were noted in clinical response, maintenance of remission, or adverse events, although the trial was not powered to detect such differences in the individual disease groups. The results of NOR-SWITCH, together with other clinical trials with similar results,[6–16] increased the confidence of gastroenterologists to switch patients to CT-P13. The European Crohn's and Colitis Organisation has published an updated position statement[17] based on a literature search, which states that, although evidence for the efficacy and safety of switching is reassuring, more information about pharmacokinetics and immunogenicity needs to be generated.

We did a trial to investigate whether serum concentration of infliximab with CT-P13 were non-inferior to those with originator infliximab 16 weeks after switching in patients with inflammatory bowel disease and rheumatoid arthritis. In this paper, we report results for patients with inflammatory bowel disease.

Methods

Study design and participants

SECURE was an open-label, multicentre, prospective, phase 4 trial at 13 academic and non-academic sites, 11 in the Netherlands and two in Belgium. Eligible patients were aged 18 years or older; had a confirmed diagnosis of ulcerative colitis or Crohn's disease; were in clinical remission, which was defined as a score on the Simple Clinical Colitis Activity Index (SCCAI) of less than 2·5 for patients with ulcerative colitis or a score on the Harvey-Bradshaw Index (HBI) of 4 or less for patients with Crohn's disease; and on continuous treatment with originator infliximab for more than 30 weeks at dosing intervals of 7–9 weeks. Patients who were receiving combination therapy were eligible, but doses of concomitant immunomodulators had to be stable for at least 4 months. Pregnant or nursing people; those with psychiatric disorders or major comorbidities, such as severe diabetes, tuberculosis, severe infections, uncontrollable hypertension, severe cardiovascular disease (New York Heart Association class 3 or 4), or severe respiratory diseases; and those taking another biological drug or a non-registered new chemical entity were excluded. This trial was done according to the Declaration of Helsinki. The study protocol was approved by the ethics committees of all 13 study sites. All patients provided written informed consent.

Procedures

All patients were given CT-P13 at a dose and infusion duration identical to those of originator infliximab (~5 mg/kg every 7–9 weeks), according to the product information and local guidelines. Changes in dosing intervals were not permitted. One batch of CT-P13 was used to avoid bias. Patients who took antihistamines or steroids, or both, before originator infliximab infusions also took them before CT-P13. Demographics, disease characteristics, and concomitant medications were

recorded at baseline, when the first dose of CT-P13 was given. Two further study visits occurred—one at 7–9 weeks, when patients received the second infusion of study drug, and one at 14–18 weeks when they received their third infusion. Before each infusion, serum samples were collected, trough drug concentrations were measured, and clinical disease activity was scored. Patients served as their own controls on the basis of data for originator infliximab recorded at baseline. Investigators could choose to withdraw patients from the trial for medical reasons at any timepoint.

Serum concentrations of infliximab and anti-drug antibodies at all visits were measured centrally at the end of the clinical phase at Sanquin (Amsterdam, Netherlands), by in-house bridging ELISA and radioimmunoassay antigen-binding test, respectively. The radioimmunoassay antigen-binding test detects anti-drug antibodies in the absence of drug (ie, it is a drug-sensitive assay).[18,19] C-reactive protein and faecal calprotectin concentrations were measured locally. Laboratory results were not accessible to investigators during the trial. Before the study, assays of infliximab serum concentrations and anti-drug antibodies were validated.[20]

Outcomes

Our primary outcome was change in serum concentrations of infliximab between baseline and 16 weeks for ulcerative colitis and Crohn's disease separately. Secondary endpoints were CT-P13 infliximab serum concentrations 8 weeks after switching; anti-drug antibodies to infliximab at 8 weeks and 16 weeks; C-reactive protein concentrations at baseline, 8 weeks, and 16 weeks; faecal calprotectin concentrations at baseline and 16 weeks; clinical disease activity (as measured with the SCCAI in ulcerative colitis and the HBI in Crohn's disease) at baseline, 8 weeks, and 16 weeks; and quality of life measured with the generic EQ-5D questionnaire at week 16 compared with baseline. Secondary endpoints were also assessed separately in patients with ulcerative colitis and Crohn's disease.

Safety endpoints included incidence and type of adverse events, which were classified as treatment related or not treatment related and graded as mild, moderate, or severe. Adverse events were assessed up to 30 days after discontinuation.

Statistical analysis

The sample size was calculated on the basis of a coefficient of variation of 50%, an expected ratio of means of 1, a one-sided α of 0·05, a correlation of at least 0·7 between infliximab serum concentrations at baseline and 16 weeks, and a non-inferiority margin of 15%. The enrolled population was defined as all participants who provided informed consent. The full-analysis population consisted of all patients who received at least one dose of CT-P13 treatment during the study and who underwent at least one post-dose efficacy assessment. The per-protocol population included patients who received at least one dose of CT-P13 and attended at least one post-dose efficacy assessment, who did not have major protocol violations and who had available infliximab serum concentrations at baseline and 16 weeks. The safety population included all participants who received at least one dose of CT-P13 treatment and attended at least one safety assessment after that dose. We did efficacy analyses in the per-protocol population and safety analyses in the safety population. We calculated that, to achieve 90% power, 42 patients were needed per disease type in the per-protocol analysis. Assuming that 20% of patients would be excluded from the per-protocol population, a minimum of 53 patients needed to be recruited per disease type to allow for subgroup analysis with equal allocation.

The study was a non-inferiority trial, with the ratio of infliximab serum concentrations at week 16 to those at baseline as the outcome. Non-inferiority was established, at a significance level of 5%, if the lower limit of the two-sided 90% CI for the geometric mean of this ratio was above 100% minus δ (the non-inferiority margin). We used a non-inferiority margin of 15%, which is in line with the registration trials of CT-P13.[2,3] Least-squares point estimates for the geometric mean of the ratio and a two-sided 90% CI were computed per disease group. The null hypothesis was that the geometric mean of the

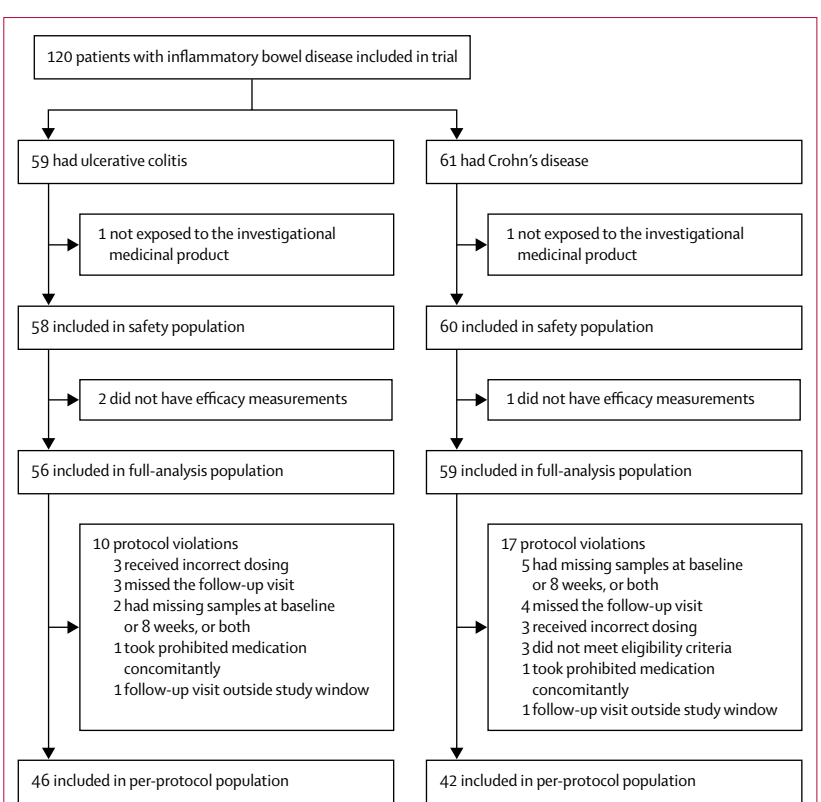

Figure 1: **Trial profile**

ratio of serum infliximab concentrations at 16 weeks to those at baseline was 85% or less, whereas the alternative hypothesis of non-inferiority was that the geometric mean of the ratios was 85%. The non-inferiority analysis was done in the per-protocol population and repeated, for sensitivity reasons, in the full-analysis population.

ANOVA of the change from baseline scores for the secondary endpoints at weeks 8 and 16 was done, and the overall within-group effect was tested. The null hypothesis was that the values for a specific endpoint would be the same at all measured timepoints. The alternative hypothesis was that, for a specific endpoint, at least one of the timepoints would differ from the others. We deemed p values less than 0·05 to be significant. If the ANOVA was significant, we did post-hoc tests to establish where these differences occurred. The assumptions of the ANOVA (eg, normality) were assessed, and, if necessary, the data were transformed. We did all statistical analysis in SAS (version 9.1.2). This study is registered with www.ClinicalTrialsRegister.eu, number 2014-004904-31.

Role of the funding source

The study funder (Mundipharma) was responsible for study design, the study protocol, and data monitoring, funded the analysis of the blood samples done by

	Ulcerative colitis (n=46)	Crohn's disease (n=42)	Inflammatory bowel disease (n=88)
Sex			
Male	21 (46%)	22 (52%)	43 (49%)
Female	25 (54%)	20 (48%)	45 (51%)
Age, years			
Mean (SD)	48·3 (16·0)	41·5 (15·7)	45·0 (16·1)
Median (IQR)	48·0 (34·0–61·0)	41·0 (28·0–50·0)	45·5 (31·5–56·0)
Range	19–84	19–73	19–84
Disease duration, years			
Mean (SD)	12·2 (8·3)	12·0 (9·5)	12·1 (8·8)
Median (IQR)	9·0 (6·7–19·2)	10·1 (4·3–16·9)	9·1 (5·7–17·9)
Range	2–39	1–37	1–39
Infliximab treatment duration, months			
Mean (SD)	52·5 (29·9)	59·3 (45·8)	55·7 (38·3)
Median (IQR)	43·2 (27·7–74·7)	41·2 (27·7–91·0)	41·8 (27·7–80·5)
Range	11–122	9–184	9–184
Immunogenicity status			
Positive	4 (9%)	0 (0%)	4 (5%)
Negative	42 (91%)	42 (100%)	84 (95%)
Combination therapy			
Overall	13 (28%)	16 (38%)	29 (33%)
Azathioprine	12 (26%)	10 (24%)	22 (25%)
Tioguanine	0 (0%)	1 (2%)	1 (1%)
Mercaptopurine	1 (2%)	2 (5%)	3 (3%)
Methotrexate	0 (0%)	3 (7%)	3 (3%)
Infliximab dose, mg/kg			
Mean (SD)	5·1 (0·5)	5·3 (1·3)	5·2 (0·9)
Median (IQR)	5·0 (5·0–5·0)	5·0 (5·0–5·0)	5·0 (5·0–5·0)
Range	5–8	4–10	4–10
Baseline faecal calprotectin, µg/g			
n	43	32	75
Mean (SD)	146·5 (344·4)	126·1 (181·1)	137·8 (284·9)
Median (IQR)	57·0 (15·0–172·0)	40·0 (24·0–188·0)	49·0 (19·0–180·0)
Range	1–2240	1–737	1–2240
Baseline C-reactive protein, mg/L			
n	46	41	87
Mean (SD)	3·0 (3·1)	5·0 (7·9)	3·9 (5·9)
Median (IQR)	2·0 (1·0–5·0)	4·0 (1·0–5·0)	3·0 (1·0–5·0)
Range	0–15	0–49	0–49

Data are n (%), unless otherwise specified.

Table 1: **Demographics and baseline characteristics of per-protocol population**

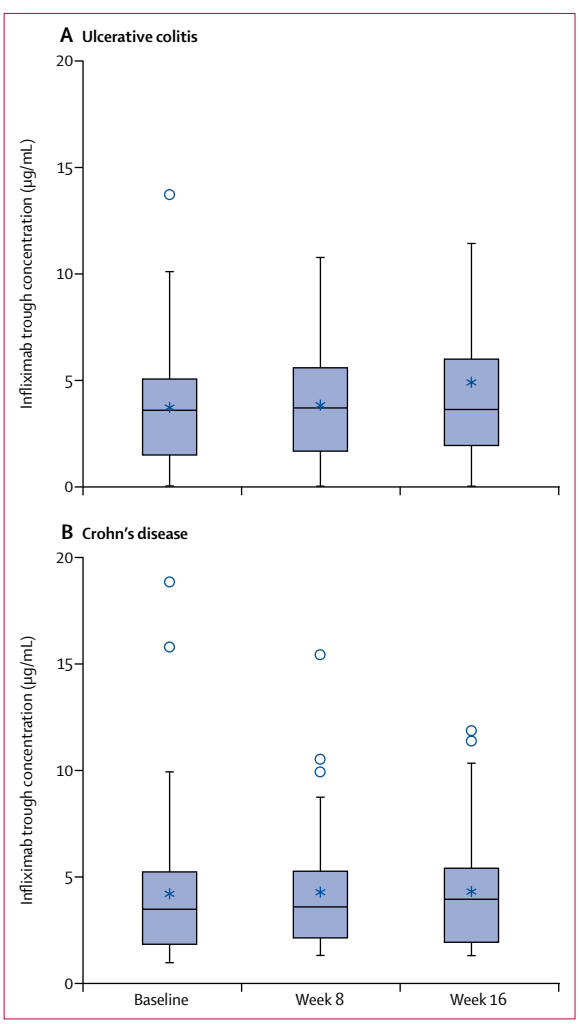

Figure 2: **Infliximab serum concentrations (per-protocol population)**
The box represents the IQR. The line in the middle of the box represents the median. The asterisk represents the mean. The whiskers represent the maximum (ie, 1·5 times higher than the 75th percentile) and minimum (1·5 times lower than the 25th percentile) values. The circles outside the whiskers represent outliers. (A) Patients with ulcerative colitis. One outlier of serum infliximab concentration of 52·46 mg/mL at week 16 is not shown. (B) Patients with Crohn's disease.

independent laboratories and the statistical analyses done by an independent statistician, and was involved in data interpretation and in writing of the report. The corresponding author had access to all study data and final responsibility for the decision to submit for publication.

Results

Between June 5, 2015, and April 6, 2017, we recruited 120 consecutive patients with inflammatory bowel disease: 59 with ulcerative colitis and 61 with Crohn's disease (figure 1). 115 patients were included in the full-analysis population, 118 were included in the safety population, and 88 were included in the per-protocol population—46 (52%) with ulcerative colitis and 42 (48%) with Crohn's disease (figure 1). In the ulcerative colitis group, the mean age was 48·3 years (SD 16·0), 21 patients (46%) were male, and median disease duration was 9·0 years (IQR 6·7–19·2; table 1). In the Crohn's disease group, mean age was 41·5 years (SD 15·7), 22 patients (52%) were male, and median disease duration was 10·1 years (IQR 4·3–16·9; table 1).

The median serum concentration of infliximab was 3·6 μg/mL (IQR 1·5–5·1) at baseline and 3·6 μg/mL (IQR 1·9–5·0) at week 16 in patients with ulcerative colitis (figure 2A). The ratio of infliximab concentration at week 16 to that at baseline was 110·1% (90% CI 96·0–126·3). In patients with Crohn's disease, the median infliximab concentration was 3·5 μg/mL (IQR 1·8–5·2) at baseline and 4·0 μg/mL (IQR 1·9–5·4) at week 16 (figure 2B). The corresponding ratio of infliximab concentrations was 107·6% (90% CI 97·4–118·8). In both populations, the lower bound of the 90% CI of the geometric mean of the ratio of the infliximab concentrations was higher than 85%, the prespecified non-inferiority ratio. Median serum concentrations of infliximab at week 8 were 3·7 μg/mL (IQR 1·7–5·0) in the ulcerative colitis population (figure 2A), and 3.6 μg/mL (IQR 2·1–5·2) in the Crohn's disease population (figure 2B).

Median C-reactive protein concentrations at week 8 and week 16, and median faecal calprotectin concentrations at week 16, did not differ from those at baseline (figure 3; table 2; appendix). In the ulcerative colitis group, based on SCCAI scores, 35 (76%) participants were in clinical remission at week 16, seven (15%) were in partial remission, and three (7%) had a relapse (scores were not available for one participant). In the Crohn's disease group, based on HBI scores, 37 (88%) participants were in clinical remission at week 16, three (7%) patients had mild disease activity, and

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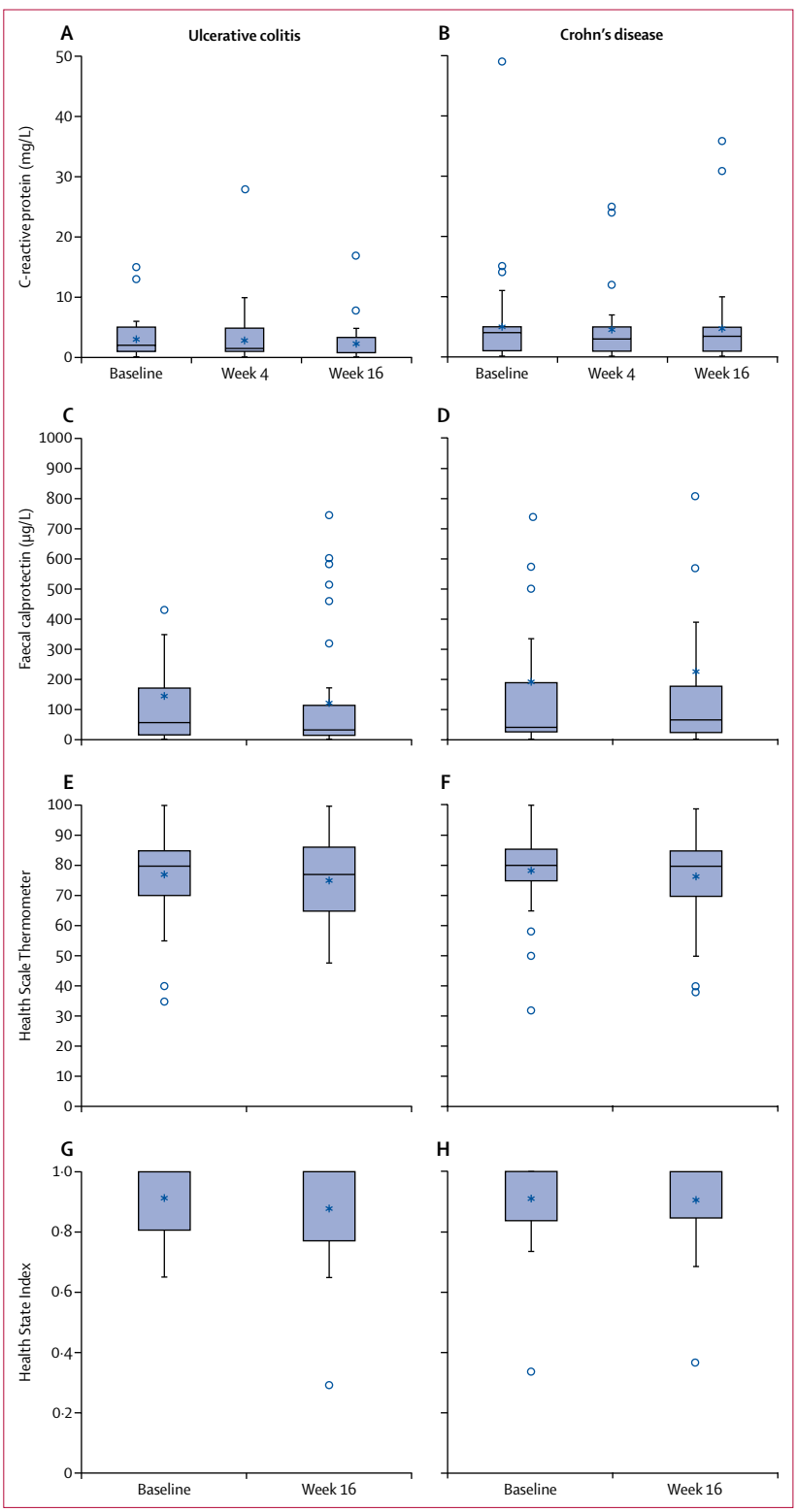

Figure 3: **Secondary outcome measures (per-protocol population)**
C-reactive protein in patients with ulcerative colitis (A) and Crohn's disease (B), faecal calprotectin in patients with ulcerative colitis (C) and Crohn's disease (D), EQ-5D Health State Thermometer in patients with ulcerative colitis (E) and Crohn's disease (F), and EQ-5D Health State Index data for patients with ulcerative colitis (G) and Crohn's disease (H). The box represents the IQR. The line in the middle of the box represents the median. The asterisk represents the mean. The whiskers represent the maximum value (1·5 times higher than the 75th percentile) and minimum (1·5 times lower than the 25th percentile) values. The circles outside the whiskers represent outliers.

	Ulcerative colitis (n=46)	Crohn's disease (n=42)	Inflammatory bowel disease (n=88)
C-reactive protein (mg/L)			
Week 8			
n	44	41	85
Mean (SD)	0·1 (4·5)	−0·3 (6·1)	−0·1 (5·3)
Median (IQR)	0·0 (0·0 to 0·0)	0·0 (−1·0 to 0·0)	0·0 (0·0 to 0·0)
Range	−12 to 23	−24 to 19	−24 to 23
Week 16			
n	44	41	85
Mean (SD)	−0·5 (3·3)	−0·2 (5·9)	−0·4 (4·7)
Median (IQR)	0·0 (−1·0 to 0·0)	0·0 (−1·0 to 0·0)	0·0 (−1·0 to 0·0)
Range	−12 to 12	−14 to 28	−14 to 28
Faecal calprotectin, µg/g			
Week 16			
n	36	26	62
Mean (SD)	−17·9 (400·6)	89·9 (263·3)	27·3 (351·2)
Median (IQR)	13·5 (−1·5 to 35·0)	3·0 (−5·0 to 116·0)	9·0 (−4·0 to 58·0)
Range	−2213 to 433	−263 to 1063	−2213 to 1063
Simple Clinical Colitis Activity Index			
Week 8			
n	46	..	..
Mean (SD)	0·5 (1·4)	..	..
Median (IQR)	0·0 (0·0 to 1·0)	..	..
Range	−2·0 to 7·0	..	..
Week 16			
n	45	..	..
Mean (SD)	0·7 (1·6)	..	..
Median (IQR)	0·0 (0·0 to 1·0)	..	..
Range	−2·0 to 6·0	..	..
Harvey-Bradshaw Index			
Week 8			
n	..	42	..
Mean (SD)	..	0·3 (1·6)	..
Median (IQR)	..	0·0 (0·0 to 1·0)	..
Range	..	−3·0 to 4·0	..
Week 16			
n	..	42	..
Mean (SD)	..	0·5 (2·0)	..
Median (IQR)	..	0·0 (0·0 to 1·0)	..
Range	..	−3·0 to 7·0	..
EQ-5D health state thermometer			
Week 16			
n	40	41	81
Mean (SD)	−1·9 (10·2)	−2·2 (12·1)	−2·1 (11·1)
Median (IQR)	0·0 (−10·0 to 5·0)	0·0 (−10·0 to 5·0)	0·0 (−10·0 to 5·0)
Range	−20 to 20	−35 to 22	−35 to 22
EQ-5D health state index			
Week 16			
n	45	42	87
Mean (SD)	−0·03 (0·1)	−0·01 (0·1)	−0·02 (0·1)
Median (IQR)	0·0 (−0·1 to 0·0)	0·0 (−0·1 to 0·0)	0·0 (−0·1 to 0·0)
Range	−0·5 to 0·20	−0·3 to 0·4	−0·5 to 0·4

Table 2: **Change from baseline in secondary parameters**

two (5%) patients had moderate disease activity. Quality of life, as measured with the EQ-5D questionnaire, was similar at week 16 to that at baseline (figure 3).

In the full-analysis population, results were similar to those in the per-protocol population, except for the infliximab ratio (week 16 *vs* baseline) in participants with Crohn's disease, which did not achieve non-inferiority (appendix). One patient developed anti-drug antibodies after baseline, resulting in an unmeasurable infliximab serum concentration at week 16 (data not shown). This outlier in the dataset substantially affected non-inferiority.

Five (4%) of the 118 patients in the safety population were positive for anti-drug antibodies at baseline and in remission (four in the ulcerative colitis population and one in the Crohn's disease group). All five patients remained positive for anti-drug antibodies during the study, but this persistent positivity was not associated with loss of clinical response, and the trial was finished according to protocol. The four patients with ulcerative colitis were included in the per-protocol population (table 3), but the patient with Crohn's disease was excluded because their dose of study drug was incorrect. Three patients (one in the ulcerative colitis population and two in the Crohn's disease population) in whom anti-drug antibodies were not detected at baseline had detectable antibodies at 16 weeks in the full-analysis population (appendix).

250 adverse events were reported in the safety population (table 4). Six serious adverse events were reported in six patients. Two of these adverse events (both perianal abscesses) were related to disease worsening, but only one was deemed treatment related. One patient with ulcerative colitis had been previously diagnosed with an adenocarcinoma of the appendix, which was treated successfully at that time. During the trial, two metastases were detected and surgically removed. Two other patients with ulcerative colitis also underwent surgery, one for benign lymphadenopathy and one for carpal tunnel syndrome. One patient with Crohn's disease who had a serious adverse event discovered she was pregnant after signing the informed consent form, and chose to have an abortion. Although not included in the per-protocol analysis, this patient was included in the safety analysis. The remaining five patients with serious adverse events were included in the per-protocol analysis, because the adverse event did not affect study treatment.

Discussion

In this open-label, multicentre, phase 4 non-inferiority study, we showed that serum concentrations of infliximab 16 weeks after initiating CT-P13 were non-inferior to those at baseline in patients with inflammatory bowel disease who were in remission and had previously been taking infliximab. The chosen sample size allowed subgroup analysis per disease group, and thus non-inferiority was also established individually for both ulcerative colitis and Crohn's disease.

	Ulcerative colitis (n=46)	Crohn's disease (n=42)	Inflammatory bowel disease (n=88)
Baseline			
Anti-drug antibody negative	42 (91%)	42 (100%)	84 (95%)
Anti-drug antibody positive	4 (9%)	0 (0)%)	4 (5%)
Week 8			
Anti-drug antibody negative	39 (85%)	40 (95%)	79 (90%)
Anti-drug antibody positive	5 (11%)	0 (0%)	5 (6%)
Missing data	2 (4%)	2 (5%)	4 (5%)
p value	>0·999	>0·999	..

The p values were calculated with McNemar's test.

Table 3: **Antibodies to infliximab**

	Ulcerative colitis (n=58)	Crohn's disease (n=60)	Inflammatory bowel disease (n=118)
Patients with at least one adverse event	48 (83%)	46 (77%)	94 (80%)
Adverse events	118	132	250
Patients with at least one treatment-related adverse event	21 (36%)	18 (30%)	39 (33%)
Treatment-related adverse events	30	34	64
Patients with at least one severe adverse event	2 (3%)	3 (5%)	5 (4%)
Severe adverse events	2	6	8
Patients with at least one treatment-related severe adverse event	0 (0%)	1 (2%)	1 (1%)
Treatment-related severe adverse events	0	1	1
Patients with at least one serious adverse event	3 (5%)	3 (5%)	6 (5%)
Serious adverse events	3	3	6
Patients with at least one treatment-related serious adverse event	0 (0%)	1 (2%)	1 (1%)
Treatment-related serious adverse events	0	1	1
Deaths	0	0	0

Data are n (%) or n. Adverse events were treatment related if investigators suspected a causal relation with the investigational product. Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) as mild, moderate, or severe. Serious adverse events were defined as any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, required hospital admission or prolonged an existing hospital stay, resulted in persistent or significant disability or incapacity; or caused a congenital anomaly or birth defect (in the child of a person who was exposed to CT-P13). Any other medically important event or reaction could also be considered a serious adverse event when, based upon appropriate medical judgment, the event could jeopardise the patient or could require an intervention to prevent one of the outcomes listed above. Adverse events that were coded as severe were not necessarily classed as serious adverse events.

Table 4: **Overall summary of adverse events during CT-P13 treatment (safety population)**

Our results are similar to those of previous studies[5,11,21] in which no changes were noted in serum concentrations after switching from originator infliximab to a biosimilar. In Smits and colleagues' prospective observational cohort study[11] in 83 patients with inflammatory bowel disease (24 with ulcerative colitis, 57 with Crohn's disease, and two with unclassified disease), no significant effects on short-term clinical, biochemical, and pharmacokinetic outcomes were detected after switching to CT-P13. Furthermore, our findings were similar to those of the largest randomised clinical trial so far, NOR-SWITCH,[5] which included 482 patients with different autoimmune diseases, including inflammatory bowel disease. Non-inferiority in infliximab serum concentration was shown for the total enrolled patient population after switching. No differences were noted in clinical, biochemical, and pharmacokinetic outcomes, and the frequency of adverse events was similar between those remaining on originator infliximab and those who switched to CT-P13. In a non-interventional trial,[21] Schmitz and colleagues also noted no significant differences in serum infliximab concentrations, inflammatory markers, and clinical disease activity before and after switching from originator infliximab to CT-P13. By contrast with these studies, the SECURE trial was powered to show non-inferiority in individual diseases.

Besides non-inferiority of infliximab serum concentrations, we noted no significant differences in quality of life and clinical remission before and after switching to CT-P13. In both ulcerative colitis and Crohn's disease, a proportion of patients were not in clinical remission at the end of the trial (24% and 12%, respectively), and two patients with Crohn's disease developed perianal abscesses. Because clinical remission was an inclusion criterion, disease status could only either remain the same or worsen. Even a slight increase in clinical scores from complete clinical remission to mild disease activity (ie, SCCAI scores >2·5 or HBI scores >4) was deemed a loss of clinical response. In NOR-SWITCH,[5] disease worsening occurred in both the CT-P13 and originator infliximab groups within a year (in 26% and 30% of participants, respectively), showing that disease worsening is common in patients with inflammatory bowel disease treated with infliximab. Our data are similar to those from previously mentioned trials.[8–15,21]

We noted no differences in immunogenicity (ie, formation of anti-drug antibodies) before or after switching. Five patients were positive for anti-drug antibodies at inclusion, and remained positive during the study. Nevertheless, these patients remained in clinical remission without symptoms. Three patients developed anti-drug antibodies, in line with NOR-SWITCH,[5] in which new anti-drug antibodies developed in both the infliximab originator (7%) and CT-P13 (8%) groups. However, treatment duration and tests for anti-drug antibodies were different in both trials. One of the patients who developed anti-drug antibodies during our trial had very low trough concentrations of infliximab at baseline and two patients had undetectable trough concentrations at inclusion, with no detectable antibodies measured with a drug-sensitive assay, an assay that only detects anti-drug antibodies in the absence of drug. At the second study visit, antibodies to infliximab were detectable and signs of loss of response were noted. These antibodies were probably not newly developed because of the switch to CT-P13, and would also have become detectable if patients remained on originator infliximab. Although subtle immunogenic changes cannot be detected with a drug-sensitive assay,

they are probably not clinically relevant. In this trial, the same validated assays for serum drug measurements and anti-drug antibodies were used for both originator infliximab and CT-P13. Similarity was shown by Gils and colleagues[22] between the ELISAs used to measure serum concentrations of originator and biosimilar infliximab. Patients included in the SECURE trial were stable and had a long disease and treatment history. Future trials should address whether there is an increased immunogenicity risk if patients switch to biosimilar infliximab in the early phase of treatment, or after switching between different biosimilars.

Our study has several limitations. It did not have a control group in which patients continued originator infliximab. However, because we measured serum infliximab concentrations at baseline before initiation of CT-P13, patients could serve as their own controls, and therefore interpersonal variability in pharmacokinetics could be kept to a minimum. Our study population might not be optimally representative of the entire inflammatory bowel disease population in hospitals, because only those in clinical remission who were stable on maintenance therapy were included. Results might be different for patients with active disease. Follow-up was short in our study—16 weeks. However, we chose this period because we hypothesised that major pharmacokinetic changes in infliximab serum concentrations would occur shortly after switching. One of the strengths of this trial is the heterogeneity of the population, which is a result of the trial being done in both academic and non-academic hospitals. Another strength is that we collected information about quality of life before and after switching, in addition to clinical and biochemical data.

In conclusion, serum concentrations of infliximab 16 weeks after switching to CT-P13 were non-inferior to those at baseline in patients with stable ulcerative colitis and Crohn's disease. Switching patients with inflammatory bowel disease who are in clinical remission to CT-P13 is efficacious and well tolerated.

Contributors

ASS wrote the Article. GRD contributed to and supervised Article preparation. All authors were involved in data analysis and approved the final version of the Article.

SECURE study group members

Filip J Baert (AZ Delta, Roeselare, Belgium), Reinhard Bos (Medisch Centrum Leeuwarden, Leeuwarden, Netherlands), Gerard Dijkstra (Universitair Medisch Centrum Groningen, Groningen, Netherlands), Frank Hoentjen (Radboud Universitair Medisch Centrum, Nijmegen, Netherlands), Marc R Kok (Maasstad Ziekenhuis, Rotterdam, Netherlands), Lindy-Anne Korswagen (Sint Franciscus Gasthuis, Rotterdam, Netherlands), Frank J G M Kubben (Maasstad Ziekenhuis, Rotterdam, Netherlands), Marieke J Pierik (Maastricht Universitair Medisch Centrum, Maastricht, Netherlands), Petra A J M Vos (Amphia Ziekenhuis, Breda, Netherlands), Rachel L West (Sint Franciscus Gasthuis, Rotterdam, Netherlands), Janneke van der Woude (Erasmus MC, Rotterdam, Netherlands).

Declaration of interests

ASS has received lecture fees from Merck Sharp & Dohme, Takeda, AbbVie, Tillots, Pfizer, and Mundipharma. PJJB has received educational grants from AbbVie and Janssen, speaker fees from AbbVie and Takeda, and advisory board fees from Hospira, Janssen, Merck Sharp & Dohme, Mundipharma, Roche, Pfizer, Takeda, and Dr Falk Benelux. MN has received institutional research support consultancy fees, or speaker fees from Pfizer, Abbvie, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Mundipharma, UCB, Janssen, Menarini, Eli Lilly, Celgene, and Abbvie. TR has received honoraria for lectures from Pfizer, Abbvie, and Regeneron, and a research grant from Genmab. GRD has served as adviser for Abbvie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boerhinger Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Ferring, Dr Falk, Engene, Galapagos, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millennium, Takeda, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Novonordisk, Pfizer, Prometheus Laboratories, Nestlé, Protagonist, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor, and received speaker fees from Abbvie, Ferring, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Shire, Millenium, Takeda, Tillotts, and Vifor. JPJB-M and YJBvM are employees of Mundipharma. All other authors declare no competing interests.

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