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Title: Real-world use of therapeutic drug monitoring of CT-P13 in patients with inflammatory bowel disease: A 12-month prospective observational cohort study.

Short title: Real-world use of TDM

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Abbreviations: Crohn's disease: CD; ulcerative colitis: UC; inflammatory bowel disease: IBD; tumour necrosis factor-alpha: TNF; C-reactive protein: CRP.

Conflicts of interest:

Laurent Beaugerie received consulting fees from Janssen, Pfizer, and Allergan; lecture fees from Abbvie, Janssen, MSD, Ferring Pharmaceuticals, Mayoly-Spendler, Takeda, and Tillots; and research support from Abbott, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD and Takeda.

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Matthieu Allez received honoraria from Novo Nordisk, MSD, Abbvie, Ferring, Genentech, Janssen, Pfizer, GSK, Hospira, UCB, Novartis, Takeda, and Mayolo-Spindler.

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Abstract

Background: Whether therapeutic drug monitoring (TDM) of infliximab should be implemented in daily practice is an ongoing controversy.

Aims: To assess the real-world use of TDM in an observational multicentre cohort study with consecutive patients with inflammatory bowel disease (IBD) treated with CT-P13.

Methods: Between September 2015 and December 2016, 364 patients with IBD were treated with CT-P13 in 13 gastroenterology departments and were followed up for 54 weeks. Disease activity, CT-P13 trough concentration and anti-CT-P13 antibody (ACA) were recorded.

Results: Steroid-free clinical remission rates at week 54 were 67.0% and 56.4% in patients with CD and UC, respectively. CT-P13 trough concentrations were measured in 70.7% of the patients. The mean CT-P13 trough concentration was 4.2 ± 4.3 $\mu\text{g/mL}$. The presence of ACA was observed in 53 (15.9%) patients. CT-P13 trough concentration was collected in a proactive approach in 62.8% of cases and in a reactive approach in 37.2%. Among patients who submitted to TDM, CT-P13 therapy was optimized in 88.7% of the reactive group and in 22.5% of the proactive group ($p < 0.001$).

Conclusion: In a real-world cohort of patients with IBD treated with CT-P13, more than two-thirds of the patients underwent TDM. CT-P13 optimization was much less common in the proactive approach than in the reactive approach.

Introduction

Inflammatory Bowel disease (IBD) is a chronic and disabling condition involving the gastrointestinal tract^{1,2}. The advent of anti-TNF agents have dramatically changed treatment paradigms in IBD, increasing physicians' expectations regarding treatment from a simple control of clinical activity to mucosal/histological healing and prevention of disability³⁻⁵. Accordingly, anti-TNF agents are widely prescribed in patients with IBD, which represents a major part of IBD-related health care costs^{6,7}. Although the efficacy of anti-TNF agents is clearly established, up to 30% of patients do not respond to the induction therapy and up to 20% per year lose response afterwards⁸⁻¹².

Measurement of serum trough concentration for anti-TNF agents has been found to be highly relevant. Indeed, higher serum trough concentrations have been associated with better clinical and endoscopic outcomes in patients with both Crohn's disease (CD) and ulcerative colitis (UC)¹³⁻¹⁵. Although there is ongoing controversy about the preemptive use of therapeutic drug monitoring, adjusting the dose of the anti-TNF agent according to the serum trough concentration has been associated with better clinical outcomes and has been implemented in clinical practice¹⁶⁻¹⁸.

Recently, the infliximab patent expired, thereby creating the opportunity for developing biosimilar products. The infliximab biosimilar CT-P13, with the trade names INFLECTRA® (HOSPIRA Inc.) and REMSIMA® (SERVIER Lab.), has been granted a marketing authorization for the treatment of all indications for which reference infliximab is approved based on the results of head-to-head phase 1 and 3 randomized controlled trials in anti-TNF naïve patients with rheumatologic diseases¹⁹⁻²¹. The Assistance Publique – Hôpitaux de Paris (AP-HP) is a consortium of university hospitals in the Paris – Ile-de-France area, comprising 39 different hospitals and groups of hospitals, including 13 gastroenterology departments treating patients with IBD. In September 2015, the consortium signed a public

contract with HOSPIRA Inc. to replace infliximab with the biosimilar CT-P13. In the same contract, HOSPIRA also proposed reimbursement of CT-P13 serum concentration dosage 2 times per year for each patient treated with CT-P13.

The systematic use of the infliximab biosimilar CT-P13 in all consecutive patients starting infliximab therapy from September 2015 in our institutions gave us the opportunity to assess the effectiveness and safety of CT-P13 in a large cohort of patients with IBD treated with CT-P13. More importantly, it allowed us to study the use of therapeutic drug monitoring (TDM) of CT-P13 therapy in a real-world setting.

PATIENTS AND METHODS

Study population

From September 2015 to December 2016, we conducted a multicentre, retrospective, observational, usual care cohort study in 13 gastroenterology departments belonging to AP-HP. All consecutive patients starting CT-P13 for active IBD were eligible for inclusion. Active IBD was defined according to the Harvey-Bradshaw index (HBI) >4 for CD patients and the Mayo Clinic score ≥ 6 for UC patients or according to the use of steroids (prednisone or methylprednisolone ≥ 20 mg per day or budesonide > 6 mg per day)²². Exclusion criteria included loss to follow-up during the 14-week induction period, switch from reference infliximab to CT-P13, extraintestinal manifestation without significant IBD activity as the initial indication for CT-P13, treatment with CT-P13 for prevention of CD postoperative recurrence or pouchitis, presence of an ostomy and pregnancy or lactation. Patients were recruited from the pharmacy database and/or the standardized hospital inpatient diagnostic dataset including ICD-10 codes. All patients received written information about the study. Patients accepting the switch were then included in the present study and followed-up until week 54. The protocol was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS n° 16-249) and the Commission Nationale de l'Informatique et des Libertés (CNIL n° 1955334) commission. No commercial entity had any role in the study. All authors had access to the study data and reviewed and approved the final manuscript.

Patient demographic and clinical characteristics were collected from medical records and included age at diagnosis, gender, smoking habits, CD location and behaviour according to the Montreal classification, UC extent according to the Montreal classification, extraintestinal manifestation, smoking habits, history of medical and surgical treatment of IBD and familial history of IBD²³.

Patients received intravenous CT-P13 at a dose of 5 mg per kg at weeks 0, 2 and 6 and then every 8 weeks thereafter through week 54²⁴⁻²⁶. Concomitant use of steroids and/or immunomodulators including azathioprine, 6-mercaptopurine or methotrexate was permitted. No standardized protocol for steroid tapering and immunomodulatory maintenance was established. In patients who did not respond to CT-P13 therapy, the treating physician was free to optimize CT-P13 therapy by increasing the dose of CT-P13 up to 10 mg per kg and/or by reducing the infusion interval up to every 4 weeks through week 54.

Follow-up

All of the patients submitted to a standardized follow-up protocol, consisting of: a physical examination; calculation of HBI or partial Mayo clinic score for CD and UC patients, respectively; CRP (mg/L), haemoglobin (g/dL), leukocyte (/10⁹/L) and platelet (/10⁹/L) counts; and data collection on adverse events^{27,28}. The evaluations were performed at weeks 14, 22, 30 and 54. All adverse events were recorded. Endoscopic evaluations were suggested between week 30 and 54 but were not mandatory.

CT-P13 trough concentrations and anti-CT-P13 antibody (ACA) were measured in the morning prior to the CT-P13 infusion using a validated drug-sensitive enzyme-linked immune-absorbent assay (ELISA, LISA- TRACKER Duo Infliximab, Theradiag, Croissy-Beaubourg, France). Therapeutic drug monitoring (TDM) was not mandatory, and TDM data were collected between week 14 to week 54 at the investigator's discretion in patients with either steroid-free clinical remission (proactive TDM) or inadequate response to infliximab (reactive TDM).

Steroid-free clinical remission at week 14 and 54 was defined as an HBI \leq 4 for patients with Crohn's disease and as a partial Mayo Clinic score $<$ 3 with a combined stool frequency and rectal bleeding subscore of \leq 1 for patients with ulcerative colitis²². Safety was

assessed prospectively through week 54 by the physician in charge and retrospectively collected from patient records. Adverse events were classified as severe when they led to treatment interruption, hospitalization, disability or persistent damage, colectomy or death.

Statistical Analysis

The sample size was not predefined. All of the included patients were evaluated from the inclusion visit through week 54. Patients who discontinued CT-P13 were considered non-responders in an intent-to-treat manner. The data are expressed as a number (%) for qualitative data and as a mean \pm the standard deviation (SD) or median [interquartile range] for quantitative data. The hazard ratios (HRs) are provided with 95% confidence intervals (CIs). Characteristics of patients with CD and UC were compared using chi-square and Mann-Whitney tests whenever appropriate. The proportions of patients who met the criteria for steroid-free clinical remission during the follow-up of maintenance therapy were computed relative to the whole population included at week 0. To identify the predictors of steroid-free clinical remission at week 14 and week 54, as well as therapeutic infliximab trough concentration ($> 3 \mu\text{g/mL}$), univariate analyses were performed using a chi-square test without correction for multiple testing. Subsequent multivariate analyses using binary logistic regression models were performed separately for CD and UC patients and adjusted for using the abovementioned variables with an ascending stepwise procedure using the Wald test. Quantitative values were converted to qualitative values using the dichotomy from the median value in two distinct groups of equal size. Variables with $p < 0.10$ in the univariate analysis were considered to be potential adjustment variables for the multivariate analysis. All analyses were two-tailed, and p values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS statistical software (SPSS Inc., v17, Chicago, IL, USA). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Study population

A total of 379 patients with IBD initiated CT-P13 therapy between September 2015 and December 2016 (**Figure 1**). Fifteen patients were excluded; seven were lost to follow-up during the induction period, four were treated with CT-P13 for prevention of postoperative recurrence and four were treated for pouchitis. A total of 364 patients were, therefore, included, including 230 patients with CD and 134 patients with UC and IBDU. Patient demographic data, baseline disease characteristics and medication history are listed in **Table 1**.

Steroid-free clinical remission at week 14

At week 14, 157 (67.7%) and 69 (51.5%) patients were in steroid-free clinical remission in the CD and the UC groups, respectively (**Figure 1 and table S1**). In multivariate analysis of the CD cohort data, logistic regression demonstrated that patients with a CRP level > 10 mg/L (HR = 0.44, 95%CI[0.21-0.91], p = 0.03), an HBI >10 (HR = 0.36, 95%CI[0.17-0.79], p = 0.01) and history of intestinal resection (HR = 0.46, 95%CI[0.23-0.92], p = 0.03) were less likely to achieve steroid-free clinical remission at week 14 after CT-P13 induction therapy. Patients with BMI > 21.5 kg/m² (HR = 2.04, 95%CI[1.05-4.00], p < 0.04) and uncomplicated (absence of perianal disease and/or penetrating or stricturing disease phenotype) CD phenotype (HR = 2.17, 95%CI[1.12-4.17], p = 0.02) were more likely to achieve steroid-free clinical remission at week 14 (**Table S2**). In a multivariate analysis of the UC cohort, logistic regression demonstrated that patients with a CRP level > 5 mg/L (HR = 2.86, 95%CI[1.22-67], p = 0.02) were more likely to achieve steroid-free clinical remission at week 54 (**Table S3**).

Steroid-free clinical remission at week 54

At week 54, 152 (67.0%) and 75 (57.7%) patients were in steroid-free clinical remission in the CD and the UC groups, respectively (**Figure 1 and Table S1**). In multivariate analysis of the CD cohort, logistic regression demonstrated that patients with a prior use of an anti-TNF agent (HR = 0.53, 95%CI[0.30-0.93], p = 0.03) and an HBI >10 (HR = 0.15, 95%CI[0.06-0.37], p < 0.001) were less likely to achieve steroid-free clinical remission at week 54 (**Table S5**). In a multivariate analysis of the UC cohort, logistic regression demonstrated that patients with an E3 phenotype according to the Montreal classification (HR = 2.63, 95%CI[1.28-5.56], p = 0.009) were more likely to achieve steroid-free clinical remission at week 54 (**Table S5**).

Therapeutic drug monitoring between week 14 and week 54

A total of 333 CT-P13 trough concentrations were measured in 236 patients at different timepoints between week 14 and week 54, accounting for 150 (69.4%) patients with CD and 86 (72.9%) with UC who were still being treated at week 14 (p = 0.54). One hundred thirty-six patients had only one CT-P13 trough concentration measurement, whereas 89 had two and eight had three. CT-P13 trough concentration data were collected from patients with steroid-free clinical remission (proactive TDM) in 209 (62.8%) patients, including 32 (15.3%) at week 14, 30 (14.4%) at week 22, 28 (13.4%) at week 30 and 119 (56.9%) between week 38 and week 54. CT-P13 trough concentrations in patients with an absence of steroid-free clinical remission (reactive TDM) were measured more prematurely in 124 (37.2%) patients including 44 (35.5%) at week 14, 30 (24.2%) at week 22, 18 (14.5%) at week 30 and 32 (25.8%) between week 38 and week 54 (p < 0.001).

The mean CT-P13 trough concentration was 4.2 ± 4.3 µg/mL. The mean CT-P13 trough concentration was higher in patients achieving steroid-free clinical remission than in patients who did not (4.8 ± 4.2 vs. 3.2 ± 4.3 , p = 0.001). The distribution of CT-P13 trough concentration is listed in **Table 2**. No difference was found according to the time of CT-P13

trough concentration collection ($p = 0.97$). The mean CT-P13 trough concentration was higher in patients with UC than in those with CD (5.0 ± 4.7 vs. 3.7 ± 3.9 , $p = 0.005$).

To examine therapeutic CT-P13 trough concentration ($> 3 \mu\text{g/mL}$), we separately analysed patients with UC and CD. In multivariate analysis of patients with CD, patients with the presence of ACA (HR = 0.11 95%CI[0.03-0.39], $p = 0.001$), male gender (HR = 0.47 95%CI[0.25-0.92], $p = 0.03$), CRP > 10 mg/L (HR = 0.27 95%CI[0.12-0.60], $p = 0.001$) and uncomplicated CD phenotype (HR = 0.44 95%CI[0.23-0.87], $p = 0.02$) were less likely to present with therapeutic CT-P13 trough concentration $> 3 \mu\text{g/mL}$ (**Table 3**). In the multivariate analysis of patients with UC, patients with the presence of ACA (HR 0.08 95%CI[0.02-0.41], $p = 0.02$) were less likely to present with therapeutic CT-P13 trough concentration $> 3 \mu\text{g/mL}$, whereas patients with prior optimization of CT-P13 therapy by either increasing the infusion dose or reducing the infusion interval (HR = 5.56 95%CI[2.18-14.29], $p < 0.001$), steroid-free clinical remission at the time of TDM (HR = 2.55 95%CI[1.11-5.85], $p = 0.03$) and concomitant steroids at the time of CT-P13 introduction (HR = 3.98 95%CI[1.48-10.75], $p = 0.006$) were more likely to reach therapeutic CT-P13 trough concentration (**Table 4**).

The presence of ACA was observed in 53 (15.9%) patients. No difference was found between patients with CD and UC (18.2% vs. 12.3%, $p = 0.18$). The rate of patients achieving steroid-free clinical remission was higher in patients with absence of ACA compared with those with presence of ACA (65.7% vs. 47.2%, $p = 0.01$).

Among the 124 patients in the reactive TDM group, CT-P13 therapy was optimized in 110 (88.7%) by increasing the dose and/or reducing the infusion interval in 73 (58.9%), adding immunosuppressant in four (3.2%), switching to another anti-TNF agent in 19 (15.3%) and swapping to either vedolizumab, ustekinumab or surgery in 14 (11.3%). Among the 209 patients in the proactive group, CT-P13 therapy was optimized less frequently than in the

reactive group ($p < 0.001$) in 47 patients (22.5%) by increasing the dose and/or reducing the infusion interval in 38 (18.2%), and because of positive ACA by adding immunosuppressant in four (1.9%), switching to another anti-TNF agent in one (0.5%) and swapping to either vedolizumab or ustekinumab in four (1.9%).

A total of 97 out of 236 patients (41.1%) had at least two CT-P13 trough concentration measurement, including 51 (40.8%) with a previous CT-P13 trough concentration $\leq 3 \mu\text{g/mL}$ and 46 (41.4%) with a previous CT-P13 trough concentration $> 3 \mu\text{g/mL}$ ($p=0.94$). The median delay between the two dosages was 28.9 ± 14.9 weeks. There was a trend for a shorter delay in patients with a previous CT-P13 trough concentration $\leq 3 \mu\text{g/mL}$ (25.9 ± 12.9 vs. 32.1 ± 16.3 , $p = 0.06$).

Safety

An analysis of adverse events was performed for all patients who received at least one dose of CT-P13 (**Table 5**). Adverse events occurred in 93 (25.5%) out of 364 patients. Serious adverse events occurred in 39 (10.7%) patients and were mainly related to IBD exacerbation in 23 cases. Four patients developed neoplasia during follow-up: two with colorectal cancer, one with non-Hodgkin lymphoma, and one with ovarian cancer. Adverse events of infection occurred in 31 patients accounting for 35 adverse events of infection, including upper respiratory tract infection in 10, pharyngitis in 5, flu or flu-like infection in 5, gastrointestinal infection in 5, rhinopharyngitis in 4 and other infections in 4. Thirteen infusion reactions were reported.

DISCUSSION

Whether TDM should be implemented in daily clinical practice is an ongoing controversy^{29,30}. Herein, we provide the first study assessing real-world use of TDM in patients with active IBD treated with CT-P13 and one of the largest cohort studies assessing CT-P13 trough concentration. At the end of the 54-week study period, more than two-thirds of the patients with CD and more than half of the patients with UC experienced steroid-free clinical remission. In the meantime, two-thirds of the patients had at least one measurement of CT-P13 trough concentration, which included two-thirds of the patients in a proactive setting.

Our work shows that CT-P13 exposure is highly correlated with steroid-free clinical remission in patients both with CD and UC (**Table 2**). After excluding patients with mechanistic failure of CT-P13, defined as absence of steroid-free clinical remission despite adequate CT-P13 trough concentration ($> 7 \mu\text{g/mL}$), the correlation was even stronger (**Table S6**). We also observed differences in exposure profiles linked to the type of IBD with higher CT-P13 exposure in patients with UC, despite a lower efficacy. Whether these differences could be overcome by increasing the dose of CT-P13 early during the induction phase remains questionable.

The mechanism of resistance to infliximab is in part due to the immune-mediated formation of the anti-infliximab antibody^{30,31}. Based on the analysis of randomized controlled trials and observational studies, rates of anti-infliximab antibody formation are extremely variable, ranging from 0% to 65.3%³¹. This observed range may be reduced to 5% to 30% when using data from large studies with at least 200 patients. In this study, 15.9% of patients with IBD treated with CT-P13 presented ACA. The presence of ACA was associated with a significant reduction in CT-P13 exposure (1.2 ± 3.3 vs. 4.7 ± 4.2 , $p < 0.001$), but with a lower rate of steroid-free clinical remission (47.2% vs. 65.7%, $p = 0.01$). Those results are in the lower range compared to those of previous studies. Most of our patients were treated with

concomitant immunosuppressant, which may have limited the formation and impact of ACA. It is necessary to mention the inability of the assay used in our study to detect ACA in the presence of a significant concentration of CT-P13 (> 1-2 µg/mL), as in many similar studies¹⁶.

The concept of reactive TDM is now widely recognized. Indeed, patients could be categorized into two groups: those with mechanistic failure and those with inadequate drug exposure due to immune-mediated mechanisms and/or high inflammatory burden³⁰. Benefits of reactive TDM have been suggested in observational studies and in one small RCT³²⁻³⁷. Proactive TDM implies optimizing anti-TNF therapy and possibly switching to another biological agent in patients with quiescent disease²⁹. Such strategy has been evaluated in two randomized controlled studies: the TAXIT trial in patients with IBD on long-term maintenance infliximab therapy and the TAILORIX trial in biologic-naïve patients with early CD starting infliximab in combination with an immunosuppressant^{17,18}. Both studies were negative for their primary outcome, which were clinical and biological remission at week 54 for the TAXIT trial and sustained clinical, biological and endoscopic remission at week 54 for the TAILORIX trial. More recently, another randomized controlled study in 78 children with CD has shown superiority of proactive TDM of adalimumab compared with reactive monitoring³⁸. In the present study, more than two-thirds of the patients still treated after week 54 were monitored based on trough CT-P13 concentration trough week 54. Among those monitored patients, two-thirds were monitored in a proactive approach while in steroid-free clinical remission. However, only 22.5% of patients monitored in a proactive approach had CT-P13 optimization. These results might reflect reluctance of physicians to use proactive TDM. In that setting, the CT-P13 trough concentration measurement is performed to allow further optimization in the case of loss of response.

Our study has several strengths, including the large number of patients, the multicentre design, the exhaustivity of the inclusions based on the pharmacy database and the low rate of

loss to follow-up (2.5%). CT-P13 infusions were performed in a day-hospital allowing the collection, even retrospectively, of all clinical and biological data to evaluate disease activity. Real-world studies are often criticized when compared with data from randomized controlled trials. However, only one-third of patients with moderate to severe IBD would have been eligible to participate in such randomized controlled trials³⁹. Randomized controlled trials also have selection bias by selecting patients with a more severe disease phenotype who might agree to participate in the trial to obtain an experimental treatment. They may also attract patients with less severe disease who may be tempted by intensive monitoring. Our study has also some limitations considering its retrospective nature and the absence of standardization of TDM and endoscopic assessment.

In conclusion, our results confirm the effectiveness and safety of CT-P13 after a 54-week follow-up period allowing more than two-thirds of patients with CD and more than half of patients with UC to achieve steroid-free clinical remission. CT-P13 exposure predicted efficacy of CT-P13 in patients both with CD and UC. In a real-world setting, more than two-thirds of patients underwent TDM, one-third in a reactive approach and two-thirds in a proactive approach. However, optimization of CT-P13 therapy was noted in almost all patients in the reactive group, but in only one-quarter of patients in the proactive group. Prospective studies continue to be warranted to demonstrate the benefits of routine, proactive TDM over prospective dosage of CT-P13 trough concentration in anticipation of a subsequent loss of response.

Table legend

Table 1: Demographic and baseline disease characteristics and medication histories of 274 patients with active inflammatory bowel disease treated with CT-P13.

Table 2: Proportions of patients with various CT-P13 trough concentration cut-offs in 333 patients treated with CT-P13 maintenance therapy measured between week 14 and week 54, according to the type of inflammatory bowel disease.

Table 3: The predictors associated with therapeutic infliximab trough concentration ($> 3 \mu\text{g/mL}$) between week 14 and week 54 in 203 patients with Crohn's disease with CT-P13.

Table 4: The predictors associated with therapeutic infliximab trough concentration ($> 3 \mu\text{g/mL}$) between week 14 and week 54 in 130 patients with ulcerative colitis with CT-P13.

Table 5: Adverse events affecting 149 patients with inflammatory bowel disease treated with CT-P13 therapy after the week 54 visit

Figure legend

Figure 1: Flowchart of the study

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**Patients with active IBD
treated with CT-P13 between September 2015 and December 2016
n = 279**

**Crohn's disease
n = 240**

**Ulcerative colitis
n = 139**

10 excluded
Lost to follow-up (n = 6)
Prevention of postoperative
recurrence (n = 4)

6 excluded
Lost to follow-up (n = 1)
Pouchitis (n = 4)

230 on CT-P13 therapy

**Week 0
n = 274**

134 on CT-P13 therapy

CT-P13 5 mg per kg at weeks 0, 2 and then every 4-8 weeks

14 discontinued
Primary non-response (n = 6)
Infusion-related reaction (n = 7)
Rectal carcinoma (n = 1)

18 discontinued
Primary non-response (n = 15)
Infusion-related reaction (n = 1)

216 on CT-P13 therapy

**Week 14
n = 344**

118 on CT-P13 therapy

23 discontinued
Loss of response (n = 22)
Non-hodgkin lymphoma (n = 1)

20 discontinued
Loss of response (n = 16)
Infusion-related reaction (n = 4)

193 on CT-P13 therapy

**Week 30
n = 291**

98 on CT-P13 therapy

23 discontinued
Loss of response (n = 17)
Pregnancy (n = 2)
Ovarian carcinoma (n = 1)
Miscellaneous (n = 4)

22 discontinued
Loss of response (n = 21)
Paradoxical reaction (n = 1)

170 on CT-P13 therapy

**Week 54
n = 246**

76 on CT-P13 therapy

Table 1: Demographic and baseline disease characteristics and medication histories of 274 patients with active inflammatory bowel disease treated with CT-P13.

Patient's characteristics	Crohn's disease (n = 230)	Ulcerative colitis (n = 134)	Total (n = 364)	p
Age at inclusion, years	<u>32.6 (25.3-46.1)</u>	<u>37.3 (26.8-54.8)</u>	<u>33.6 (25.9-48.7)</u>	0.02
Male gender, no (%)	119 (51.7%)	63 (47.0%)	182 (50.0%)	0.48
BMI, kg/m²	<u>21.5 (19.4-24.8)</u>	<u>22.7 (20.2-25.6)</u>	<u>21.9 (19.7-25.3)</u>	0.04
Smoking habits, no (%)				
Past smoker	43 (18.7%)	46 (36.3%)	89 (24.5%)	0.001
Active smoking	73 (31.7%)	12 (9.0%)	85 (23.4%)	<0.001
Disease duration, (years)	<u>5.7 (1.2-12.8)</u>	<u>3.5 (1.2-7.7)</u>	<u>4.5 (1.2-10.9)</u>	0.005
History of intestinal resection	66 (28.7%)	0	66 (18.1%)	-
Extra intestinal manifestations	45 (19.6%)	9 (6.7%)	54 (14.8%)	0.001
Familial history of IBD	37 (16.1%)	18 (13.4%)	55 (15.1%)	0.55
Age at diagnosis	<u>24.2 (19.0-35.2)</u>	<u>30.0 (22.3-46.2)</u>	<u>25.7 (19.5-38.8)</u>	<0.001

A1: ≤16 years	28 (12.2%)	9 (6.7%)	37 (10.2%)	0.11
A2: 17 – 40 years	166 (72.2%)	86 (64.2%)	252 (69.2%)	0.13
A3: > 40 years	36 (15.7%)	39 (29.1%)	75 (20.6%)	0.003
Crohn's disease, no (%)				
Disease location, no (%)				
Ileal	98 (42.6%)	-	-	-
Colonic	44 (19.1%)	-	-	-
Ileocolonic	86 (37.4%)	-	-	-
Upper GI tract	14 (6.1%)	-	-	-
Disease phenotype, no (%)				
Non structuring – Non penetrating	94 (40.9%)	-	-	-
Stricturing	65 (28.3%)	-	-	-
Penetrating	71 (30.9%)	-	-	-
Perianal disease, no (%)	34 (14.8%)	-	-	-
Harvey Bradshaw-index	<u>6.0 (4.0-8.3)</u>	-	-	-
Ulcerative colitis, no (%)				

Proctitis	-	12 (9.0%)	-	-
Left-sided colitis	-	39 (29.1%)	-	-
Pancolitis	-	83 (61.9%)	-	-
Mayo Clinic score	-	<u>8.0 (7.0-10.0)</u>	-	-
Partial Mayo Clinic score	-	<u>6.0 (5.0-8.0)</u>	-	-
Mayo endoscopic subscore	-	<u>2.0 (1.0-3.0)</u>	-	-
UCEIS	-	<u>5.0 (4.0-6.0)</u>	-	-
Prior treatment				
Immunosuppressant :	156 (67.8%)	75 (56.0%)	231 (63.5%)	0.02
Azathioprine	151 (65.7%)	72 (53.7%)	223 (61.3%)	0.03
Methotrexate	20 (8.7%)	7 (5.2%)	27 (7.4%)	0.30
anti-TNF :	105 (45.7%)	40 (29.9%)	145 (39.8%)	0.004
Infliximab	28 (12.2%)	4 (3.0%)	32 (8.8%)	0.002
Adalimumab	88 (38.3%)	28 (20.9%)	116 (31.9%)	0.001
Vedolizumab	7 (3.0%)	5 (3.7%)	12 (3.3%)	0.77
Concomitant medications at week 54				

Steroids	67 (29.1%)	96 (71.6%)	163 (44.8%)	<0.001
Immunosuppressants	155 (67.4%)	93 (69.4%)	248 (68.1%)	0.73
Biologic variables				
Leukocytes count, 10 ⁹ /L	<u>8500 (6200-10280)</u>	<u>8660 (6920-11475)</u>	<u>8520 (6525-10957)</u>	0.19
Hemoglobin level, g/L	<u>12.5 (11.4-13.7)</u>	<u>12.1 (10.8-13.2)</u>	<u>12.4 (11.2-13.5)</u>	0.02
Platelets count, 10 ⁹ /L	<u>335 (274-452)</u>	<u>317 (252-452)</u>	<u>333 (264-452)</u>	0.88
CRP level, mg/L	<u>15.0 (4.8-39.0)</u>	<u>17.0 (5.0-46.3)</u>	<u>16.0 (5.0-42.0)</u>	0.35
serum albumin, g/L	<u>36.0 (32.0-39.8)</u>	<u>35.8 (31.0-40.0)</u>	<u>36.0 (31.0-40.0)</u>	0.46

BMI: body mass index; CRP: high sensitivity C-reactive protein; IBDU: Inflammatory bowel disease unclassified; GI: gastrointestinal; IBD: inflammatory bowel disease; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

Variables are presented as n (%) and median (interquartile range).

P values are based on a two-sided chi-square test for all categorical variables and on Mann-Whitney test for all quantitative variables.

Table 2: Proportions of patients with various CT-P13 trough concentration cut-offs in 333 patients treated with CT-P13 maintenance therapy measured between week 14 and week 54 according to the type of inflammatory bowel disease

	Week 14 to 54					
	Crohn's disease (n = 203)			Ulcerative colitis (n = 130)		
Infliximab trough concentration	Steroid-free clinical remission (n = 134)	No steroid-free remission (n = 69)	P	Steroid-free clinical remission (n = 75)	No steroid-free remission (n = 55)	p
> 1 µg/mL	104 (77.6%)	29 (42.0%)	<0.001	65 (86.7%)	37 (67.3%)	0.01
> 3 µg/mL	70 (52.2%)	21 (30.4%)	0.004	47 (62.7%)	24 (43.6%)	0.03
> 7 µg/mL	23 (17.2%)	11 (15.9%)	0.99	25 (33.3%)	12 (21.8%)	0.17
> 10 µg/mL	13 (9.7%)	7 (10.1%)	0.99	15 (20.0%)	6 (10.9%)	0.23

Variables are presented as n (%).

P values are based on a two-sided chi-square test.

Table 3: The predictors associated with therapeutic infliximab trough concentration (> 3 µg/mL) between week 14 and week 54 in 203 patients with Crohn’s disease with CT-P13.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Presence of anti-infliximab antibody	0.11 (0.04-0.32)	< 0.001	0.11 (0.03-0.39)	0.001
CRP > 10 mg/L	0.25 (0.12-0.50)	< 0.001	0.27 (0.12-0.60)	0.001
Male gender	0.50 (0.28-0.87)	0.02	0.47 (0.25-0.92)	0.03
Steroid-free clinical remission	2.50 (1.35-4.63)	0.004		
Platelets > 280 /mm ³	0.51 (0.28-0.92)	0.03		
Uncomplicated phenotype	0.56 (0.32-0.98)	0.05	0.44 (0.23-0.87)	0.02

CRP: C-reactive protein; HR: hazard ratio; CI: confidence interval. HR with 95% confidence interval (CI) was estimated using binary logistic regression.

Table 4: The predictors associated with therapeutic infliximab trough concentration (> 3 µg/mL) between week 14 and week 54 in 130 patients with ulcerative colitis with CT-P13.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Optimization of infliximab therapy	2.69 (1.29-5.59)	0.008	5.56 (2.18-14.29)	< 0.001
Presence of anti-infliximab antibody	0.09 (0.02-0.43)	0.002	0.08 (0.02-0.41)	0.02
Steroid-free clinical remission	2.17 (1.07-4.41)	0.02	2.55 (1.11-5.85)	0.03
partial Mayo Clinic score >5	6.21 (1.29-30.30)	0.02	-	NS
Steroids at the time of CT-P13 introduction	2.85 (1.28-6.33)	0.01	3.98 (1.48-10.75)	0.006
Concomitant immunosuppressant at the time of CT-P13 introduction	2.12 (0.94-4.78)	0.07	-	NS

CRP: C-reactive protein; HR: hazard ratio; CI: confidence interval. HR with 95% confidence interval (CI) was estimated using binary logistic regression.

Table 5: Adverse events affecting 364 patients with inflammatory bowel disease treated with CT-P13 therapy after the week 54 visit

Event	Crohn's disease (n = 230)	Ulcerative colitis (n = 134)	Overall (n = 364)
Adverse event	64 (27.8%)	29 (21.6%)	93 (25.5%)
Number of adverse events	53	22	75
Headache	0	0	0
Paresthesia	0	0	0
IBD exacerbation	17	10	27
Paradoxical skin manifestation	2	0	2
Infusion-related reaction	10	3	13
Arthralgia	2	5	7
Vertigo	0	0	0
Miscellaneous	2	2	4
Any serious adverse event*	24 (10.4%)	15 (11.2%)	39 (10.7%)
Infectious adverse event	22 (9.6%)	9 (6.7%)	31 (8.5%)
Number of infectious adverse event	26	9	35

Rhinopharyngitis (n of events)	1	3	4
Upper respiratory tract infection (n of events)	8	2	10
GI infection (n of events)	4	1	5
Flu or Flu-like infection (n of events)	5	0	5
Sinusitis (n of events)	0	0	0
pharyngitis (n of events)	4	1	5
Miscellaneous (n of events)	4	0	4
Any serious infection	3 (1.3%)	3 (2.2%)	6 (1.6%)
Any cancer	3 (1.3%)	1 (0.7%)	4 (1.1%)

The study period included any adverse event from the week 0 visit to the week 54 visit. Patients with more than one adverse event were as separate events. *A serious adverse event was defined as any adverse event when leading to treatment interruption, hospitalization, disability or persistent damage, colectomy and death.