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ORIGINAL RESEARCH

Infliximab biosimilar CT-P13 therapy is effective and safe in maintaining remission in Crohn's disease and ulcerative colitis – experiences from a single center

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ABSTRACT

Background: CT-P13, the first biosimilar monoclonal antibody to infliximab (IFX), has been confirmed to be efficacious in inducing remission in inflammatory bowel diseases (IBD). The aim of this study was to evaluate the long-term efficacy and safety of CT-P13 therapy in Crohn's disease (CD) and ulcerative colitis (UC), and to identify predictors of sustained clinical response during a 54-week CT-P13 treatment period.

Patients and methods: Patients with CD and UC, who were administered CT-P13, were prospectively enrolled. Clinical response was assessed at week 14 and week 54. Predictive factors for disease outcome at week 54 were evaluated.

Results: 57 CD and 57 UC patients were included; 55 CD and 49 UC patients completed the induction therapy and 50 CD and 46 UC patients completed the 54-week treatment period. Clinical remission was achieved in 65.5% of CD and 75.5% of UC patients at week 14. Rate of continuous clinical response was 51% in both CD and UC at week 54. None of the examined parameters were predictive to the clinical outcome neither in CD, nor in UC.

Conclusion: This study confirmed the long-term efficacy and safety of CT-P13 therapy in IBD. Response rates at week 54 were similar in CD and UC.

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KEYWORDS
Crohn's disease; ulcerative colitis; CT-P13; biosimilar; long-term efficacy; predictors

1. Introduction

CT-P13, a biosimilar of infliximab (IFX), was the first monoclonal antibody biosimilar approved by the European Medicines Agency. Following the two pivotal clinical trials that confirmed the efficacy of CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis [1,2], data became available on short-term response to CT-P13 in inflammatory bowel diseases (IBDs). However, considering the number of full articles published in this topic, experience with the biosimilar IFX, mainly with long-term use, is still limited. We have already published an 8-week data of the efficacy of CT-P13 IFX biosimilar in Crohn's disease (CD) and ulcerative colitis (UC), and the multicenter Hungarian study has also confirmed the effectiveness and safety of CT-P13 therapy in the induction of clinical response and remission on large number of IBD patients very soon afterwards [3,4].

The ACCENT and ACT trials were the landmark randomized controlled trials demonstrating clearly that the originator IFX can maintain remission after inducing response in both diseases [5,6]. Considering the initial data on the similar short- and mid-term efficacy of the biosimilar product, it is entitled to suppose that long-term efficacy may also be comparable to the reference drug. However, confirmation data are still missing in the field of IBD. It should also not be forgotten that initially several national societies have raised concerns regarding the use of biosimilars in extrapolated indications [7]. Therefore, data from clinical studies on the comparable efficacy are extremely important and required both in induction and maintenance therapy, even if the cost-effectiveness of the biosimilar drug compared to the originator one is well known.

The aim of the present study was to evaluate the long-term clinical efficacy and safety of CT-P13 therapy in CD and UC and to identify the predictive factors of loss of response (LOR) in this study population.

2. Patients and methods

2.1. Study design and patients

This was a prospective observational study conducted between June 2014 and September 2016 at the 1st Department of Medicine, University of Szeged. Patients 18 years of age and older diagnosed with CD and UC, who were administered CT-P13, were enrolled. Eligible Crohn's patients had moderate-to-severe therapy-refractory or steroid-dependent luminal disease or therapy-refractory simple fistulizing disease or complex fistulas. Patients with UC had therapy-refractory, steroid-dependent, or moderate-to-severe acute steroid-refractory colitis. Clinical outcome was

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estimated at fixed appointments throughout the 54-week treatment period. Medical records analyzed included patients' demographic and clinical characteristics, presence of extraintestinal manifestations, previous surgeries, smoking and family history, previous history of originator IFX administration, concomitant medications, response to CT-P13, and adverse drug reactions. According to the national regulation, none of the patients received IFX treatment with the originator compound within 12 months before initiation of the biosimilar IFX.

2.2. Assessments of response to CT-P13 and end points

CT-P13 5 mg/kg was given as an intravenous infusion at weeks 0, 2, and 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. Clinical disease activity was assessed by the Crohn's Disease Activity Index (CDAI) [8] and the partial Mayo (pMayo) Scoring System in UC [9] at weeks 0, 2, 6, 14, 22, 30, 46, and 54. Continuous clinical response (CCR) was defined as a maintained response through week 54 without intermediate relapse. CD response was defined as a >100-point decrease in CDAI. UC response was defined as >30% decrease in the activity index and a decrease in rectal bleeding and endoscopy subscores. Remission was defined as CDAI below 150 for luminal CD, and for UC, it was defined as a pMayo score ≤2, with no individual subscores >1. The severity of perianal CD was evaluated by Perianal Disease Activity Index (PDAI) [10]. Clinical response was defined by a decrease of 50% or more in the number or amount of fistula discharge, and clinical remission was defined as a complete closure of fistulas. Fistula closure was defined as no drainage, either spontaneous or with gentle compression. Primary nonresponse was defined as a failure to achieve clinical response following the induction phase of CT-P13. LOR was defined as an increase in CDAI of at least 70 points in CD and an increase in the pMayo score of 2 or more with an absolute pMayo score of 4 or higher. The primary end points were CCR and clinical remission during the 54-week therapeutic period. The secondary end points were clinical and biochemical responses and safety evaluated at weeks 14 and 54. A further secondary end point was the identification of predictors of sustained clinical response during 54-week CT-P13 treatment period.

2.3 Assessment of laboratory parameters, serum drug and antibody levels, and fecal calprotectin concentrations

CT-P13 trough levels and antibody titers (ATI) as well as C-reactive protein (CRP) level, leukocyte, hematocrit, platelet count, and serum albumin were determined at every visit. Fecal calprotectin was measured by using lateral flow assay at weeks 2, 6, and 46. Enzyme-linked immunosorbent assay was applied to determine CT-P13 trough levels and ATI (LISA TRACKER, Theradiag, France). Cutoff value for CRP was 5 mg/l, and for fecal calprotectin, it was 300 µg/g. The detection cutoff value of CT-P13 trough level was 0.1 µg/ml, while 3–7 µg/ml was defined as therapeutic. The standard cutoff value of ATI level was 10 ng/ml. ATI positivity was defined above the cutoff value of ATI level.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation and are compared among groups with Mann–Whitney *U*-test; categorical variables are presented as frequency (percentage) and are compared among groups with Fisher's exact test. The examined variables in CD were CT-P13 trough levels at weeks 2, 6, and 14; antibody positivity at weeks 2, 6, and 14; CRP level at baseline and at weeks 2, 6, 14, 30, and 46; fecal calprotectin at weeks 2, 6, and 46; concomitant steroid and azathioprine therapy at the time of induction therapy and at week 30; previous use of antitumor necrosis factor (TNF) drug; and need of dose intensification. In UC, examined variables consisted of CT-P13 trough levels at weeks 2, 6, 14, 30, and 46; antibody positivity at weeks 2, 6, 14, 30, and 46; CRP level at baseline and at weeks 2, 6, 14, 30, and 46; fecal calprotectin at weeks 2, 6, and 46; concomitant steroid and azathioprine therapy at the time of induction therapy and at week 30; previous use of anti-TNF drug; and need of dose intensification.

Confidence intervals (CIs) for proportions were calculated with the Clopper–Pearson method. The changes from baseline in continuous variables (e.g. CRP, fecal calprotectin, CDAI, and pMayo score) were compared using paired-samples *t*-tests.

For the multivariate modeling of response, logistic regression was used with L2-penalization selected with Tsai's corrected AIC [11]. Results are visualized as odds ratios on log scale with 90%, 95%, and 99% CIs (using different shading). The significance was set at $p < 0.05$.

2.5. Ethical approval

Ethical approval was acquired from the National Ethical Committee 929772–2/2014/EKU [292/2014]).

3. Results

3.1. Patient population and disease activities

Fifty-seven CD and the same number of UC patients were included of which 55 CD and 49 UC patients completed the induction therapy and 50 CD and 46 UC patients completed the 54-week treatment period. In CD, the indication of CT-P13 therapy was luminal disease in 38, fistulizing disease in 12 cases, and both luminal and fistulizing diseases in 7 cases. In UC, therapy was started due to either acute onset or severe flare-up in 32 and chronic refractory activity in 25 patients. Previous anti-TNF therapy was administered for seven CD (three originator IFX and four adalimumab) and nine UC (six originator IFX, two adalimumab, and one golimumab) patients. In CD, previous anti-TNF therapy resulted in remission in two cases and in UC in six patients. Demographic data and clinical characteristics of all of the enrolled patients and those who completed week 54 are detailed in Tables 1 and 2.

Table 1. Demographic data and clinical characteristics of the patients enrolled in the study.

	CD patients (n = 57)	UC patients (n = 57)
Mean age at diagnosis (years)	28 (10–55)	31 (15–65)
Mean disease duration (years)	9 (0–27)	7 (0–22)
Male/female ratio	31/26	29/28
Smoking history		
• – Ex-smoker	5	5
• – Current smoker	13	1
• – Never smoked	26	19
• – No data	3	8
Family history for IBD	2	2
Surgical history		
• – Bowel resection	17	0
• – Fistula/abscess surgery	18	0
• Colectomy	1	1
Location/extent		
• – Ileal	7	0
• – Colonic	16	0
• – Ileocolonic	26	0
• – Upper GI	1	0
• – Ileocolonic + upper GI	7	0
• – Extensive colitis	0	27
• – Left-sided colitis	0	25
• – Proctitis	0	5
Behavior		
• – Inflammatory	19	0
• – Stenotizing	17	0
• – Penetrating	21	0
Extraintestinal manifestation		
• – Arthralgia/arthritis	14	15
• – Erythema nodosum/ pyoderma	8	3
– gangrenosum	0	2
– Scleritis/episcleritis/uveitis		
Previous medications		
– 5-Aminosalycilates	36	48
– Corticosteroids	43	48
– Thiopurines	51	42
– Cyclosporine	0	6
– Anti-TNF-α	7	9
Efficacy of previous anti-TNF-α therapy		
• – Remission	2	6
• – Response	0	0
• – No response/loss of response	5	2
• – Allergy	0	1
Concomitant medications at induction		
• – 5-Aminosalycilate	17	37
• – Corticosteroids	21	35
• – Thiopurines	34	26

UC: ulcerative colitis; CD: Crohn's disease; TNF: tumor necrosis factor; IBD: inflammatory bowel disease; GI: Gastrointestinal tract.

Table 2. Demographic data and clinical characteristics of the patients completed week 54.

	CD patients (n = 50)	UC patients (n = 46)
Mean age at diagnosis (years)	28 (10–55)	30.5 (17–65)
Mean disease duration (years)	9 (0–27)	8 (0–22)
Male/female ratio	27/23	24/22
Smoking history		
• – Ex-smoker	5	8
• – Current smoker	13	1
• – Never smoked	30	30
• – No data	2	7
Family history for IBD	2	4
Surgical history		
• – Bowel resection	15	0
• – Fistula/abscess surgery	16	0
• – Colectomy	1	1
Location/extent		
• – Ileal	6	0
• – Colonic	14	0
• – Ileocolonic	23	0
• – Upper GI	1	0
• – Ileocolonic + upper GI	6	0
• – Extensive colitis	0	21
• – Left-sided colitis	0	22
• – Proctitis	0	3
Behavior		
• – Inflammatory	17	0
• – Stenotizing	15	0
• Penetrating	18	0
Extraintestinal manifestation		
• – Arthralgia/arthritis	10	11
• – Erythema nodosum/ pyoderma	6	2
• – gangrenosum	1	1
• – Scleritis/episcleritis/uveitis		
Previous medications		
• – 5-Aminosalycilates	29	40
• – Corticosteroids	37	41
• – Thiopurines	44	35
• – Cyclosporine	0	6
• – Anti-TNF-α	5	7
Efficacy of previous anti-TNF-α therapy		
• – Remission	1	4
• – Response	0	0
• – No response/loss of response	4	2
• – Allergy	0	1
Concomitant medications at induction		
• – 5-Aminosalycilate	16	29
• – Corticosteroids	18	29
• – Thiopurines	30	22

3.2. Response to CT-P13 therapy

3.2.1. Response to the induction phase, primary nonresponse

Of the 55 CD patients who completed induction therapy, clinical response was achieved in 53 patients (96.4%) (95% CI, 87.5–99.6] – remission in 36 and partial response in 17 patients. Two patients showed primary nonresponse at week 14; their therapy was stopped. In UC, 49 patients completed induction therapy. Clinical response was achieved in 48 patients (97.9%) (95% CI, 89.1–99.9) at week 14 – remission in 37 and partial response in 11 patients. Three patients underwent colectomy before week 14: two of them because of nonresponse to the therapy and one because of the diagnosis of colonic dysplasia. At week 14, colectomy was required in one further patient due to nonresponse.

3.2.2. CCR during the maintenance phase, LOR

CCR was shown in 28 (50.9%) (95% CI, 22.2–48.6) CD patients at week 54. Of the 50 patients who completed week 54, 31 patients (62%) (95% CI, 48.6–80.4) were in clinical remission, 9 showed partial response, and 10 at active disease at week 54 (20%) (95% CI, 9.6–37.3). Twenty-three patients showed LOR between weeks 14 and 54. The overall rate of primary nonresponse and LOR during the therapy was 43.9% (95% CI, 26.0–52.4). Steroid was administered in four, dose escalation

was used in six, and combined steroid therapy and dose escalation was given in four patients with LOR. Five patients required surgical intervention, two of them underwent ileocecal resection, one patient underwent right hemicolectomy, and two needed perianal abscess surgery. CT-P13 therapy was continued in three of the operated patients after the surgery. No intervention was applied in three cases with LOR. Considering patients who required CT-P13 therapy because of perianal fistulas and completed week 54, partial response was achieved in five patients and remission with complete closure of all of the fistulas was achieved in four patients. Three patients showed LOR with continuous fistula discharge. At week 54, 15 patients stopped CT-P13 therapy based on the decision of the physician.

In UC, CCR was detected in 25 (51%) (95% CI, 23.4–51.7) patients at week 54. Of the 46 patients who completed the 54-week treatment period, 30 patients (65.2%) (95% CI, 40.6–76.3) were in remission, nine patients showed partial response, and seven patients at active disease (15.2%) (95% CI, 7.2–36.4) at week 54. LOR occurred in 22 patients after the induction therapy. Steroid was given in five, dose escalation was used in seven, and steroid and dose escalation was combined in six patients. No intervention was applied in four patients. One of the patients did not respond to dose escalation and had to be operated on before achieving week 54. The overall rate of primary nonresponse and LOR was 40.4% (95% CI, 20.8–47.9) at week 54. At week 54, the gastroenterologist decided to stop CT-P13 therapy for 24 patients.

In both diseases, CT-P13 therapy was stopped only in case of remission or CCR. Therapy discontinuation has always been discussed with the patients since in some cases with the same outcome therapy was continued because of the patients' previous complicated disease course, surgeries, responses to other treatments, need of dose escalation, etc. Figure 1 shows a flowchart with the number of patients enrolled in the study and completed induction and 54-week therapy.

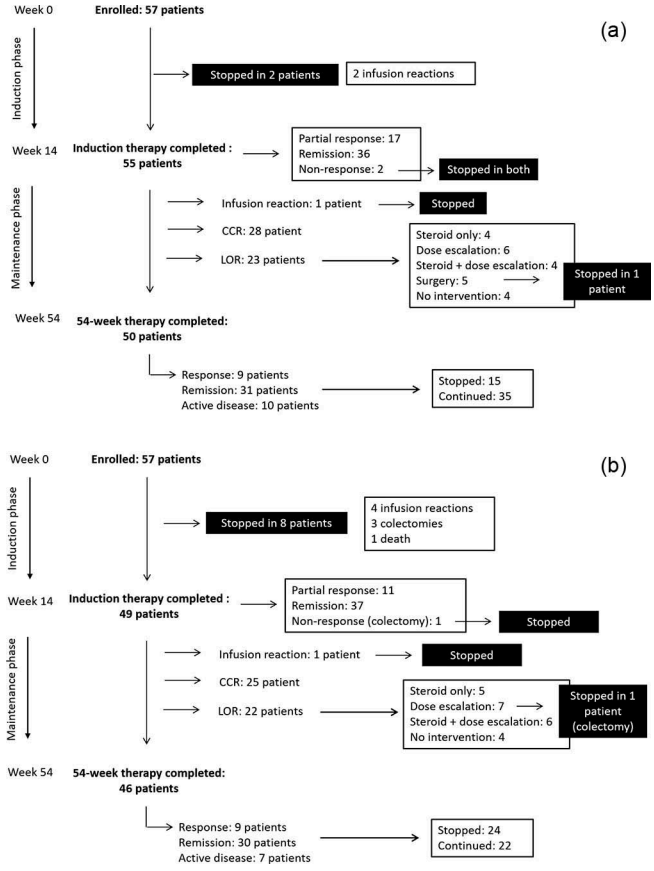

Figure 1. (a) Flow chart of CD patients enrolled in the study and completed induction and 54-week therapy. CD: Crohn's Disease, CCR: continuous clinical response, LOR: loss of response. (b). Flow chart of UC patients enrolled in the study and completed induction and 54-week therapy. UC: ulcerative colitis, CCR: continuous clinical response, LOR: loss of response.

3.3. Changes in activity scores and laboratory parameters

In CD, mean CDAI was 305.27 ± 11.2 and mean PDAI was 7.83 ± 0.6 at the beginning of CT-P13 therapy. Determination of fecal calprotectin was available in 18 CD and 17 UC patients. In CD, mean CDAI scores at weeks 14 and 54 decreased from the baseline value of 307 ± 20.1 to 106.3 ± 14.5 and 118 ± 19.8 ($p < 0.001$ in both cases). Mean PDAI scores at weeks 14 and 54 decreased from the baseline value of 10 ± 0.58 to 2.4 ± 1.3 and 3.3 ± 0.9 ($p = 0.001$ and $p = 0.003$). However, mean value of CDAI and PDAI scores did not change significantly in patients who completed the 54-week treatment period compared to the mean values of their CDAI and PDAI scores at week 14 ($p = 0.38$ and $p = 0.29$). CRP levels dropped significantly in weeks 14 and 54 compared to the baseline values (27.7 ± 6.9 to 9.86 ± 2.8, $p = 0.01$, and to 13.7 ± 4.3, $p = 0.05$). Mean level of fecal calprotectin did not decrease significantly at week 54 (725.5–762.3 µg/g, $p = 0.38$).

In UC, mean pMayo scores at weeks 14 and 54 decreased significantly from the baseline value of 7.57 ± 0.2 to 2.33 ± 0.5 and 1.15 ± 0.39 ($p < 0.001$ in both cases). Decrease of the mean value of pMayo scores from week 14 to week 54 showed borderline significance ($p = 0.055$). CRP levels also dropped significantly in week 14 but not in week 54 compared to the baseline values (23.5 ± 7.4 to 10 ± 3.3, $p = 0.05$, and to 9.5 ± 5.9, $p = 0.07$). Mean level of fecal calprotectin decreased significantly from the baseline to week 54 (953.4–604.5 µg/g, $p \leq 0.001$). Serum CT-P13 levels measured at weeks 14 and 54 did not differ significantly between patients with CCR and secondary nonresponders neither in CD (7.34 ± 5.93 vs. 4.85 ± 5.05 µg/ml, $p = 0.2$, and 7.85 ± 9.2 vs. 4.02 ± 5.56 µg/ml, $p = 0.19$) nor in UC (6.1 ± 5.4 vs. 5.87 ± 4.58 µg/ml, $p = 0.98$, and 4.67 ± 4.59 vs. 4.9 ± 6.1 µg/ml, $p = 0.74$). Tables 3 and 4 summarize the laboratory parameters throughout the treatment period in CD and UC.

3.4. Predictors of outcome

According to univariate analysis, none of the examined parameters predicted LOR either in CD or in UC. Moreover, multivariate analysis with CRP level and CT-P13 trough level at week 14, earlier anti-TNF use, baseline steroid requirement, and dose intensification did not identify any of the variables as predictors for outcome in CD (Figure 2). In UC, CRP level, CT-P13 trough level and fecal calprotectin concentration at week 6, baseline steroid requirement, and dose intensification did

Table 3. Summary of the laboratory parameters throughout the treatment period in Crohn's disease.

	Antitumor necrosis factor drug level (μg/ml)		C-reactive protein (mg/l)		WBC (g/l)		HTC (%)		PLT (g/l)		ALB (g/l)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Week 0	0.00	0.00	10.6	31.2	7.6	3.0	310.0	134.0	40.0	9.0	44.0	7.0
Week 2	17.22	14.87	3.9	4.0	6.9	2.8	39.0	7.0	288.0	92.3	45.0	6.0
Week 6	8.904	17.23	3.55	5.4	6.1	2.4	40.0	7.0	276.0	67.0	44.0	5.0
Week 14	6.09	9.85	4.2	5.7	6.8	2.9	40.0	7.0	286.0	75.0	46.0	5.0
Week 30	2.39	6.99	6.4	10.4	6.2	2.6	40.0	6.0	256.0	133.0	45.0	5.0
Week 46	3.03	8.19	5.4	10.4	6.1	2.8	39.5	5.0	261.5	90.8	44.5	5.3

Table 4. Summary of the laboratory parameters throughout the treatment period in ulcerative colitis.

	Antitumor necrosis factor drug level (μg/ml)		C-reactive protein (mg/l)		WBC (g/l)		HTC (%)		PLT (g/l)		ALB (g/l)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Week 0	0.0	0.0	14.0	35.0	9.5	5.0	37.0	10.3	343.5	153.8	44.0	6.5
Week 2	16.5	11.3	4.9	7.4	8.0	3.7	338.0	161.0	38.0	9.0	44.0	4.0
Week 6	12.2	15.5	3.8	3.6	7.7	3.7	37.0	10.0	292.0	156.0	46.0	5.5
Week 14	5.1	5.9	3.4	4.4	7.7	5.4	39.0	8.0	317.0	144.0	46.0	5.5
Week 30	5.5	7.4	3.0	3.8	6.1	3.1	39.0	7.0	282.0	98.0	48.0	7.0
Week 46	3.2	8.9	2.7	2.2	5.9	2.7	39.0	7.0	255.0	94.0	46.0	4.5

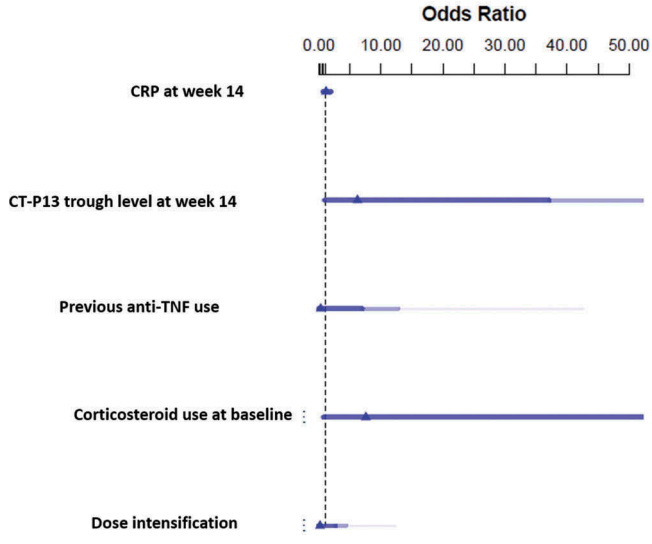

Figure 2. Multivariate analysis of patients to identify predictive factors for disease outcome in CD. Analyses included the following variables: CRP level and CT-P13 trough levels at week 14, previous anti-TNF use, dose intensification, corticosteroid use at baseline. CRP: C-reactive protein.

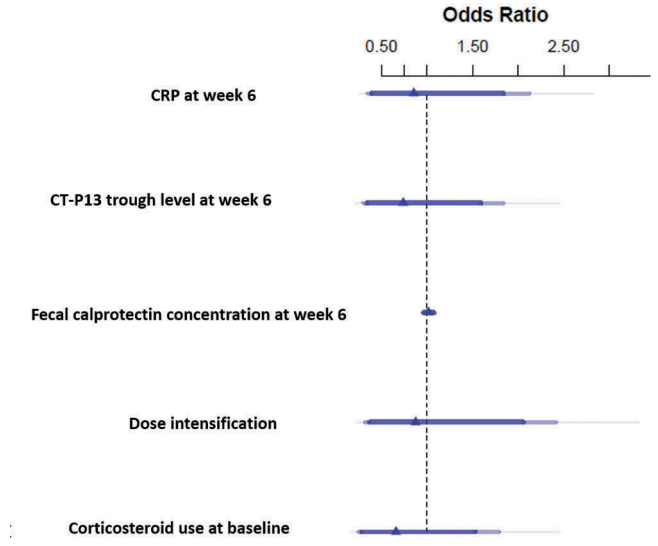

Figure 3. Multivariate analysis of patients to identify predictive factors for disease outcome in UC. Analyses included the following variables: CRP level, CT-P13 trough level and fecal calprotectin concentration at week 6, dose intensification, corticosteroid use at baseline. CRP: C-reactive protein.

not predict the disease outcome (Figure 3). No difference was observed regarding the clinical outcome at week 54 between anti-TNF-naive patients and patients previously treated with an anti-TNF agent.

3.5. Adverse events

In CD, two patients stopped CT-P13 therapy before the third infusion because of the occurrence of infusion reaction. One patient developed infusion reaction after the fourth infusion leading to therapy discontinuation. Mild infusion reaction occurred in three further patients during the 54-week period; however, CT-P13 therapy did not have to be discontinued because of this event. In UC, four patients discontinued CT-P13 therapy before week 14 because of developing infusion reaction. One patient on combo therapy died after the second infusion: the azathioprine-induced rapid and severe myelosuppression and fulminant colitis required colectomy; however, after the successful surgical intervention, fatal fungal and bacterial sepsis with neutropenia occurred. One additional patient had to stop therapy because of infusion reaction occurring after the induction phase. Infusion reaction occurred in four further UC patients after the induction phase; however, CT-P13 therapy had to be discontinued in only one of them because of the reaction.

4. Discussion

The results of this prospective observational study from our tertiary IBD center revealed CCR in 51% of CD and UC patients at week 54. Primary and secondary nonresponse occurred in about 40% of the patients. Therapy had to be discontinued as a consequence of infusion reaction in 5.3% and 7.2% of the patients. None of the examined variables proved to be predictive for long-term disease outcome in either diseases.

Widespread use of biologics has placed substantial financial burden on health-care systems all over the word. Because of the high cost of originator anti-TNF agents, interest has grown in biosimilars that are cost-effective and may sufficiently supply the reference product. CT-P13 was approved for the same indications as originator IFX. After the initial concerns about the extrapolation of clinical data from rheumatic indications to IBD, some paper has published on the efficacy and safety of CT-P13 in IBD patients. The increasing data on the comparable efficacy and safety profile may further decrease the fear of using biosimilar IFX routinely [3,12–14].

To date, most of the studies have focused on the induction phase of the therapy, and the published data regarding the efficacy and safety of long-term CT-P13 use are limited (Table 5). However, two randomized clinical trials are conducted to evaluate the safety and efficacy of CT-P13 and to demonstrate its noninferiority on long term [19,20]. Long-term data became available from a Korean study by Jung et al. [15]. Clinical response rates proved to be high, 87.5% and 100% at week 54 in anti-TNF-naive CD and UC patients representing a very favorable efficacy of CT-P13. However, if we consider responders as the number of patients who completed the induction phase of the therapy, rates of responders decrease to 21.8% of CD and 31.6% of UC. Moreover, we should be cautious when interpreting the data; the retrospective type of the study design and the small number of patients achieving week 54 provide only limited information on long-term efficacy of CT-P13. Therefore, further studies are necessary to evaluate the effect of long-term CT-P13 treatment. The recently published prospective, multicenter, cohort study by Fiorino et al. revealed that the whole efficacy in terms of induction and/or maintenance of remission/response of IFX biosimilar was high with an estimated efficacy of approximately 90% at 24 weeks [21]. In our study, response rates at weeks 14 and 54 proved to be relatively high. However, response rates are generally better in the real life compared to clinical trials, and we also should take into consideration that 36.8% and 60% of our CD patients received concomitant corticosteroid and/or immunomodulator therapy at inclusion. In UC, 61.4% and 45.6% of the patients received baseline corticosteroid and immunomodulator therapy. Both may improve therapeutic outcome at least on the short term. Notably, in the PROSIT-BIO cohort, the overall probability of response rate at week 8 was similarly high, 96.1% respectively [21].

The approval of CT-P13 for the treatment of IBD was based on the results of trials conducted in rheumatoid arthritis and ankylosing spondylitis. In the PLANETRA and PLANETAS studies, CT-P13 demonstrated equivalent efficacy and safety profile to innovator IFX at week 30, but did not provide efficacy data on long-term [1,2].

Our study prospectively reported data on the long-term outcome of CT-P13 therapy in IBD. Our results showed higher response rates in both CD and UC assessed at week 54 compared to the large randomized controlled trials of IFX, the ACCENT-1 (39%) and the ACT-1 trials (46%) [5,6].

Factors predicting to worse outcome have high clinical importance. A nationwide prospective and observational cohort study in Hungary in 210 consecutively recruited patients with CD or UC revealed that 67.2% of week 14 responder CD and 80% of week 14 responder UC patients maintained clinical response to CT-P13 at week 30 [4]. The authors demonstrated that induction treatment with the biosimilar IFX was less effective in patients previously exposed to the originator compound. Data on predictors on long-term are missing. However, the study by Gonczi et al. revealed that week 2 trough levels of CT-P13 were predictive for short-

Table 5. Summary of the studies examining the efficacy of infliximab biosimilar CT-P13 in IBD.

		Outcome at weeks 8–14		Outcome at week 30		Outcome at week 54	
Study	Number of enrolled patients	Response rates	Remission rates	Response rates	Remission rates	Response rates	Remission rates
Kang et al. [13]	8 CD, 9 UC (n = 17)	ND	CD: 25% UC: 56%	ND	ND	ND	ND
Jung et al. [15]	74 CD, 38 UC (n = 112)	CD: 90.6% UC: 81%	CD: 84.4% UC: 38.1%	CD: 95.5% UC: 91.3%	CD: 77.3% UC: 47.8%	CD: 87.5% UC: 100%	CD: 75% UC: 50%
Park et al. [16]	95 CD, 78 UC (n = 173)	CD: 84.2% UC: 75.5%	CD: 64.2% UC: 49.1%	CD: 77.8% UC: 72.2%	CD: 57.8% UC: 37%	ND	ND
Farkas et al. [3]	18 CD, 21 UC (n = 39)	CD: 37.5% UC: 20%	CD: 50% UC: 66.7%	ND	ND	ND	ND
Gecse et al. [4]	126 CD, 84 UC (n = 210)	CD: 81% UC: 78%	CD: 54% UC: 59%	CD: 67% UC: 80%	CD: 53% UC: 68%	ND	ND
Keil et al. [14]	30 CD, 22 UC (n = 52)	CD: 50% UC: 54.5%	CD: 50% UC: 40.9%	ND	ND	ND	ND
Jahnsen et al. [12]	46 CD, 32 UC (n = 78)	ND	CD: 79% UC: 56%	ND	ND	ND	ND
Smits et al. [17]	57 CD, 24 UC, 2 IBD nonclassified (n = 83)	ND	CD: 67% UC: 62% (16 weeks)	ND	ND	ND	64%
Kolar et al. [18]	90 CD, 29 UC (119) anti-TNF naive	CD: 63.3% UC: 55.2%	CD: 28.9% UC: 27.6%	ND	ND	CD: 37.5% UC: 24% (week 46)	CD: 48.6% UC: 40% (week 46)

and medium-term clinical efficacy in UC and were associated only with short-term clinical outcomes in CD [22]. In our study, we were not able to show any of the examined parameters to predict the outcome of CT-P13 therapy at week 54 neither in CD nor in UC. Fecal calprotectin concentration decreased significantly during the 54-week treatment period in UC. Neither could our study confirm whether previous anti-TNF exposure is associated with lower response rates. The lower value of the area under the Receiver Operating Characteristic (ROC) curve, the higher the false positive or false negative rates may occur. Thus, diagnostic cut-off value is not worth using in this case. However, in case of larger sample size, useful ut-off value may be reached. The relatively low number of patients treated with anti-TNF previously may result in low statistical power to reveal significant difference between the two groups.

At week 54, response rates proved to be 75.5% and 81.3% in week 14 responder CD and UC patients. According to the Hungarian multicenter study, response and remission rates at week 54 varied as 58% and 47% in CD and 64% and 53% in UC [4]. Frequency of infusion reactions was 10.5% in CD and 12.3% in UC patients, which seems to be higher compared to the existing data, although except for two, all of the patients were anti-TNF naive.

As a limitation of the study, many characteristics were compared among the CCR and LOR groups, and the reported *p*-values are not corrected for multiplicity. Therefore, these results should be used cautiously in the light of the multiple comparisons situation.

Biosimilars were introduced in the EU market in early 2015, and growing data supported the efficacy and safety of CT-P13 in IBD patients. However, except for the study of Jung et al., none of the published papers examined the therapeutic efficacy of IFX biosimilar on long term [15]. It is well known that acceptance of biosimilars in the medical community encountered some resistance. This was especially true for therapeutic indications for which no specific clinical trials with the biosimilar have been performed and that have been approved based on extrapolation. The first position statement of European Crohn's and Colitis Organisation (ECCO) on the use of biosimilars in the treatment of IBD was published in 2013 and raised some caution on the use of biosimilars [23]. ECCO called for more data on the safety and benefit of biosimilars and recommended rigorous testing in patients with IBD to ensure that appropriate efficacy and safety standards are met. ECCO also recommended making final decisions about the use of biosimilars on an individual basis. The updated ECCO position statement showed a significant shift in attitude from the previous ECCO position paper [24]. The consensus agreed on, among others, that switching from the originator to a biosimilar in patients with IBD is acceptable, and adverse events and LOR cannot be expected to be overcome with a biosimilar of the same molecule.

Moreover, while biologics have positively impacted patient treatment, their high costs may limit patient access to these medicines. The more the data we have on the efficacy on long term, the more encouraging the use of biosimilars will be. Important studies have been recently published including NOR-SWITCH and PROSIT-BIO – but week 54 data are still missing [18,25]. We believe that our study has significant additional information on long-term use of IFX biosimilars in these indications. Moreover, as strengths of the present work, data on CT-P13 levels and fecal calprotectin were also available.

Anti-TNF therapies have greatly improved outcomes in IBD, although they are not universally effective in all patients. A considerable proportion of initial responders lose response over time while others may become intolerant to these agents; therefore, there is a definite need for new therapies. However, we have long-term experience with anti-TNF agents, and an appropriate patient selection for the therapy may increase the number of responders. Moreover, early use of anti-TNF agents may change the natural course of the disease. Direct comparisons of different biologicals in IBD would help in assessing their relative efficacy, and these head-to-head studies are now in pipeline.

5. Conclusion

To the best of our knowledge, this is the first prospective study that evaluated and confirmed long-term efficacy and safety of CT-P13 therapy in IBD. Results of the randomized trials running presently may serve important data to confirm the expected safety and long-term efficacy of CT-P13, which has a significant role in supporting the use of this biosimilar drug in IBD. The wider use and the clinical benefit may ensure more patients receive effective therapy in time.

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Declaration of interest

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