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Original Article

Early Infliximab Trough Levels Predict the Long-term Efficacy of Infliximab in a Randomized Controlled Trial in Patients with Active Crohn's Disease Comparing, between CT-P13 and Originator Infliximab

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Background/Aims: The clinical efficacy and safety of CT-P13 are comparable to originator infliximab for Crohn's disease in CT-P13 3.4 study (NCT02096861). We performed a multivariate logistic analysis to demonstrate the association between early infliximab trough levels and treatment outcomes of CT-P13 and originator infliximab.

Methods: Early serum infliximab trough levels and anti-drug antibody (ADA) levels were compared between CT-P13 (n=100) and originator infliximab (n=98) groups. Receiver operating characteristic (ROC) analysis and multivariate logistic analysis were conducted to identify optimal cutoffs of serum infliximab trough levels and predictive factors for clinical outcomes.

Results: The median infliximab trough levels were not different between CT-P13 and originator infliximab groups at week 6, week 14, and in median ADA levels at week 14, respectively. ROC analysis found an infliximab concentration threshold of 4.5 μg/mL at week 6 and 4.0 μg/mL at week 14 as the cutoff value with the highest accuracy for the prediction of clinical outcomes. Serum infliximab trough levels at weeks 6 and 14 predicted clinical remission at weeks 30 and 54, and endoscopic remission at week 54. The combinations of clinical remission or C-reactive protein normalization with an early infliximab trough level improved the prediction of long-term clinical or endoscopic remission.

Conclusions: A threshold in serum infliximab trough level at week 6 and week 14 was highly predictive for long-term clinical outcomes. There were no statistical differences in serum infliximab trough levels and ADA levels between CT-P13 and originator infliximab. **(Gut Liver, Published online August 17, 2022)**

Key Words: CT-P13; Crohn disease; Infliximab trough level; Immunogenicity

INTRODUCTION

Anti-tumor necrosis factor α (anti-TNF-α) agent, such as infliximab, has been demonstrated to have clinical efficacy and adverse event for Crohn's disease (CD) patients but widespread use of anti-TNF-α agent has placed financial burden on global health care systems.[1,2] Due to the cost effectiveness and for sufficient supply, CT-P13, the first biosimilar of infliximab, was invented and approved by the European Medicines Agency in 2013 and licensed by the U.S. Food and Drug Administration in 2016. In recent studies, the non-inferiority was demonstrated in terms of the efficacy of CT-P13 compared with that of originator infliximab in CD patients as well as in efficacy of the switch

to CT-P13 from originator infliximab compared with that of originator infliximab maintenance.[3,4]

Biological agents could trigger the anti-drug antibodies (ADA) formation specific to the administered agent and ADA is associated with lower serum infliximab trough level.[5] Immunogenicity could lead to primary nonresponse up to one-third of patients, increase infusion reactions, and lead to the loss of response over time. Apparent exposure-response relationship with originator infliximab has been suggested. Higher serum infliximab levels were positively correlated with clinical outcomes. Paul *et al.*[6] reported that delta infliximab serum concentration (>0.5 μg/mL) at week 8 was the only independent risk factor associated with endoscopic remission in inflammatory bowel disease (IBD) patients (likelihood ratio, 2.02; 95% confidence interval [CI], 1.01 to 4.08; p=0.048). Papamichael *et al.*[7] investigated that infliximab serum concentration ≥2.2 (odds ratio [OR], 6.4; 95% CI, 1.5 to 27.1; p=0.011), ≥9.7 (OR, 3.6; 95% CI, 1.4 to 9.0; p=0.006), and ≥9.8 μg/mL (OR, 3.2; 95% CI, 1.3 to 7.9; p=0.011) served as an independent variable associated with biochemical, endoscopic, and histologic remission, respectively. The value of therapeutic drug monitoring of anti-TNF-α therapy has been highlighted by recent consensus statements, although the optimal drug concentrations and ADA thresholds are different according to the clinical outcomes evaluated.[8-11]

The immunogenicity and drug concentration levels of CT-P13 are expected to be similar to those of originator infliximab in CD patients.[12,13] ADA of originator infliximab in IBD patients also inhibits the action of CT-P13, suggesting cross-reactivity and similar immunogenicity of the two drugs.[14] The exposure-response relationship with CT-P13 in induction period also appears to be apparent, suggesting more favorable clinical outcomes with higher serum infliximab levels. The early infliximab trough level at week 2 was related to clinical efficacy at week 14 and week 30 in ulcerative colitis patients administered with CT-P13.[15] The cutoff value of 3.15 μg/mL at week 14 suggested steroid-free clinical remission and mucosal healing at week 14.[16] However, there are few studies that compared serum trough levels of CT-P13 and its originator drug in which contradicting results have been reported. Switching to CT-P13 from the originator infliximab in IBD patients, who achieved in clinical remission, showed non-inferiority in both serum concentration and ADA levels in SECURE trial: an open-label, multicenter, phase 4 trial.[17] In contrast, the difference of serum infliximab trough level at week 22 between the originator infliximab and CT-P13 groups were reported in non-switching cohorts patients with IBD, although the study was retrospectively designed and the sample size was too small to make the concrete conclusion.[18]

We conducted a further analysis of CT-P13 3.4 study (NCT02096861), which is an international, randomized, double-blind, phase 3 study in CD patients, to evaluate the relationship between early infliximab trough levels and treatment outcomes (both clinical remission and endoscopic remission) of CT-P13 and innovator infliximab. Furthermore, to determine predicting factors for clinical and endoscopic outcomes, clinical factors (Crohn's Disease Activity Index [CDAI] less than 150), C-reactive protein (CRP) levels, and fecal calprotectin levels at weeks 6 and 14 were evaluated.

MATERIALS AND METHODS

1. Patients

The details of CT-P13 3.4 study (between August 2014 and February 2017) were reported previously.[3] Briefly, moderate to severe CD patients who had not previously administered any biological agents were randomly assigned to study groups; CT-P13 followed by CT-P13 at week 30 (CT-P13-CT-P13 group); CT-P13 followed by originator infliximab at week 30 (CT-P13-infliximab group); originator infliximab followed by CT-P13 at week 30 (infliximab-CT-P13 group); originator infliximab followed by originator infliximab at week 30 (infliximab-infliximab group). Induction of CT-P13 or originator infliximab 5 mg/kg infusion at weeks 0, 2, and 6, and maintenance of CT-P13 or originator infliximab 5 mg/kg infusion at every 8 weeks were administered up to week 54. Of 220 patients in the previous study, 198 patients whose serum infliximab trough level were available at week 6 (pre-dose concentration at week 14) or week 14 (pre-dose concentration at week 22) and who had CDAI assessed at week 54 were included in our study (Supplementary Fig. 1).

2. Measurements and outcomes

As previous study described, clinical disease activity was measured by CDAI score. Endoscopic disease activity was measured by the Simplified Endoscopic Activity Score for Crohn's Disease.[3] Inflammatory markers were assessed by CRP level analyzed by a Roche COBAS 8000 C module analyzer (Roche Diagnostics, Indianapolis, IN, USA) at the central laboratory and fecal calprotectin level was analyzed by PPD using an enzyme-linked immunosorbent assay kit (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland). The primary endpoint was clinical remission, defined as an absolute CDAI less than 150 at week 30. The secondary endpoints were clinical remission at week 54, and endoscopic remission at week 54. We defined endoscopic remission as absolute Simplified Endoscopic Activity Score for Crohn's Disease ≤2 points.[19]

3. Serum infliximab trough level and ADA measurements

Serum infliximab levels were assessed by a quantitative assay using Gyrolab xP (Gyros Protein Technologies, Uppsala, Sweden). ADA was detected using a standard bridging assay based on enzyme-linked immunosorbent assay with acid dissociation. For ADA positive samples, neutralizing antibodies were detected using Meso Scale Discovery electrochemiluminescent immunoassay (Rockville, MD, USA) with Sera-Mag™ Streptavidin magnetic beads (Thermo Fisher Scientific, Waltham, MA, USA).

4. Statistical analysis

Patients' characteristics were described as means and standard deviations, or medians and ranges for all continuous variables. Proportions (%), and statistical analyses were used for categorical variables. To compare continuous variables, independent sample t tests (or Mann-Whitney test) were used. To compare categorical variables, chi-square tests (or Fisher exact test) were used, as appropriate. We performed a univariable logistic regression analysis for all variables, and the variables which achieved a p-value <0.05 after univariable logistic regression analysis were exported to the multivariable logistic regression analysis. Multivariate logistic regression analyses were performed to investigate the independent risk factors of clinical and endoscopic remission. Optimal cutoff values for the serum infliximab trough levels at weeks 6 and 14 were reported using receiver operating characteristic (ROC) curves by the Youden index. For the ROC curves, the area under the curves (AUC) were calculated. All statistical analyses were assessed with the SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

5. Ethics approval

The study protocol was reviewed and approved by independent ethics committees for each center. This study was approved by the institutional review boards of St. Vincent's Hospital (IRB number: VIRB-00115-004), Yonsei University College of Medicine (IRB number: 4-2014-0371), and all participating hospitals. The trial was conducted in accord with the Declaration of Helsinki and the International Conference on Harmonisation. All patients provided written informed consent.

Table 1. Baseline Patient Characteristics

Variable	CT-P13 (n=100)	Infliximab (n=98)	p-value*
Age, yr	34.0 (24.3–43.8)	32.0 (24.0–45.3)	0.871
Sex			1.000
Male	57 (57.0)	56 (57.1)	
Female	43 (43.0)	42 (42.9)	
Race			0.495
White	77 (77.0)	71 (72.4)	
Asian	23 (23.0)	26 (26.5)	
Other	0	1 (1.0)	
Smoking status			0.191
Current smoker	16 (16.0)	25 (25.5)	
Former smoker	14 (14.0)	9 (9.2)	
Never smoker	70 (70.0)	64 (65.3)	
Body mass index, kg/m^2	22.2±3.6	21.9±4.0	0.603
Disease duration, yr	4.1±4.3	5.3±7.2	0.159
Previous abdominal surgery	15 (15.0)	14 (14.3)	1.000
Previous anal surgery	12 (12.0)	9 (9.2)	0.646
Previous medical history			
Corticosteroid	35 (35.0)	27 (27.6)	0.286
Immunomodulator	76 (76.0)	74 (75.5)	1.000
Concomitant medical history			
Immunomodulator	52 (52.0)	44 (44.9)	0.324
Crohn's Disease Activity Index	300.0±49.2	296.3±55.5	0.605
SES-CD	9.7±8.1	9.8±7.8	0.865
Laboratory findings			
C-reactive protein (nmol/L)	115.5±176.6	147.9±198.9	0.338
Fecal calprotectin (μg/mg)	1,151.1±1,532.2	1,540.5±2,352.3	0.208

Data are presented as median (IQR), number (%), or mean±SD.
SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; IQR, interquartile range.
*p-value for comparing the CT-P13 and infliximab groups.

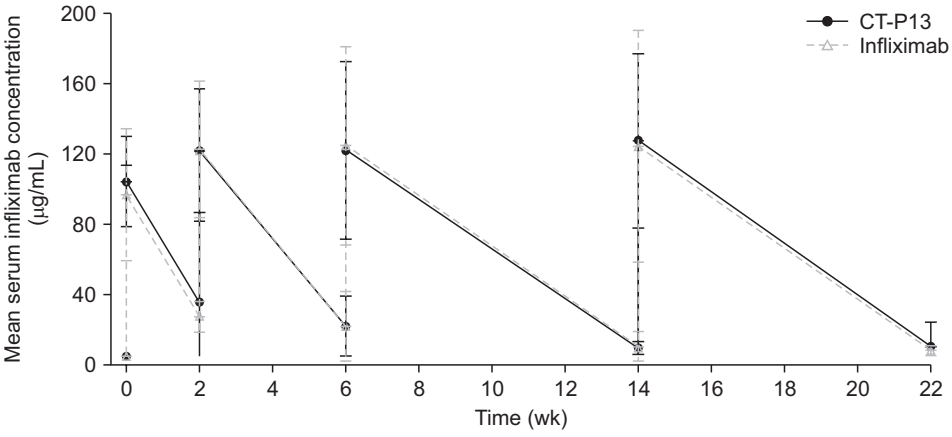

Fig. 1. Mean (standard deviation) serum concentration of infliximab.

RESULTS

1. Patient baseline characteristics, early infliximab trough levels, and ADA levels

Baseline characteristics of 198 patients (100 CT-P13 and 98 infliximab) are described in Table 1. Fifty-two patients (52.0%) in the CT-P13 group and 44 patients (44.9%) in the originator infliximab group were on concomitant immunomodulator therapy. The *post hoc* analysis showed no difference in median infliximab trough levels between CT-P13 and originator infliximab groups at week 6 (3.7 μg/mL vs 3.6 μg/mL, p=0.958) and week 14 (2.6 μg/mL vs 2.2 μg/mL, p=0.136), respectively. The mean serum concentration up to week 22 was also comparable between CT-P13 and originator infliximab groups in terms of pharmacokinetics (Fig. 1). The ADA positive rates were not different between CT-P13 and originator infliximab groups at week 14 (15.0% vs 19.4%, p=0.453). The ADA positive rates were lower in patients with concomitant immunomodulator therapy compared to those with monotherapy (9.4% vs 24.8%, p=0.005).

2. Association of clinical factors and early infliximab trough levels with clinical remission at week 30

Sixty of 100 patients (60.0%) received CT-P13 and 61 of 98 patients (62.2%) received original infliximab achieved clinical remission at week 30 (p=0.772). The mean infliximab trough levels were significantly higher in CT-P13 treated patients with clinical remission compared to patients without clinical remission at week 6 (5.04 μg/mL vs 2.24 μg/mL, p=0.006) and week 14 (3.13 μg/mL vs 0.92 μg/mL, p=0.012) (Supplementary Fig. 2A and B). Originator infliximab treated patients with clinical remission also had significantly higher mean infliximab trough levels at week 6 compared to patients without clinical remission (3.90 μg/mL vs 1.82 μg/mL, p=0.046) (Supplementary Fig. 2C). Originator infliximab treated patients with clinical remission had significantly higher infliximab trough levels at week 14 compared to patients without clinical remission, although statistically not significant (2.37 μg/mL vs 1.09 μg/mL, p=0.090) (Supplementary Fig. 2D).

The overall infliximab trough levels in responders in CT-P13 group were not statistically different from those in infliximab groups (p>0.05). Therefore, both groups were pooled for further analysis. ROC analysis found an infliximab concentration threshold of 4.5 μg/mL at week 6 (sensitivity 47.9%, specificity 71.4%) and 4.0 μg/mL at week 14 (sensitivity 35.5%, specificity 84.4%) to be significantly associated with clinical remission.

Clinical remission at week 6 (OR, 3.095; 95% CI, 1.606 to 5.967; p=0.001), and infliximab trough level >4.5 μg/mL at week 6 (OR, 2.016; 95% CI, 1.069 to 3.802; p=0.030) were independently related to clinical remission at week 30 in multivariable analysis (Supplementary Table 1). A combined ROC analysis using infliximab trough level at week 6 and clinical remission at week 6 showed an AUC of 0.690 (95% CI, 0.615 to 0.765). Clinical remission at week 14 (OR, 10.873; 95% CI, 5.113 to 23.124; p<0.001), and infliximab trough level >4.0 μg/mL at week 14 (OR, 2.335; 95% CI, 1.009 to 5.406; p=0.048) were also independently related to clinical remission at week 30 (Table 2). A combined ROC analysis using infliximab trough level at week 14 >4.0 μg/mL and clinical remission at week 14 revealed an AUC of 0.801 (95% CI, 0.737 to 0.865) (Fig. 2A).

We investigated clinical remission rates at week 30 in increments of 2 μg/mL serum infliximab trough level. Serum infliximab concentration threshold of 3 μg/mL at weeks 6 and 14 reached clinical remission rates greater than 60% (Fig. 3A and D).

3. Association of clinical factors, biochemical factors, and early infliximab trough levels with clinical remission at week 54

Sixty-six of 100 patients (66.0%) received CT-P13 and

Table 2. Factors (Baseline, Week 14) Associated with Clinical Remission at Week 30 in Crohn's Disease (Pooled Data)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Age	0.995 (0.973–1.017)	0.656		
Sex (male)	1.127 (0.632–2.008)	0.685		
Race				
White	1.000 (reference)	0.667		
Asian	1.367 (0.691–2.704)	0.368		
Other	0.000 (0.000–0.000)	1.000		
Smoking history				
Current smoker	1.000 (reference)	0.275		
Former smoker	0.649 (0.232–1.814)	0.410		
Never smoker	1.311 (0.641–2.682)	0.458		
Body mass index	1.029 (0.954–1.111)	0.453		
Disease duration	0.994 (0.948–1.043)	0.821		
Previous abdominal surgery	0.459 (0.207–1.018)	0.055		
Previous anal surgery	0.812 (0.325–2.030)	0.656		
Previous medical history				
Corticosteroid	0.730 (0.396–1.346)	0.314		
Immunomodulator	1.199 (0.618–2.325)	0.591		
Concomitant medical history				
Immunomodulator	1.517 (0.852–2.703)	0.157		
Crohn's Disease Activity Index	0.993 (0.987–0.999)	0.013†	1.001 (0.994–1.008)	0.816
SES-CD	0.998 (0.960–1.037)	0.915		
CT-P13 (vs infliximab)	1.148 (0.647–2.037)	0.637		
Baseline laboratory findings				
CRP	1.001 (0.999–1.003)	0.274		
FCP	1.000 (1.000–1.000)	0.245		
Clinical remission at week 14	11.433 (5.803–22.527)	<0.001†	0.873 (5.113–23.124)	<0.001†
Normal CRP level at week 14 (<5 mg/L)	2.424 (1.296–4.533)	0.006†	1.620 (0.762–3.444)	0.210
Normal FCP level at week 14 (<250 μg/mg)	1.745 (1.979–3.112)	0.059		
ADA level at week 14	0.877 (0.413–1.861)	0.732		
Infliximab trough level at week 14 (>4 μg/mL)	2.800 (1.362–5.747)	0.005†	2.335 (1.009–5.406)	0.048†

OR, odds ratio; CI, confidence interval; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; CRP, C-reactive protein; FCP, fecal calprotectin; ADA, anti-drug antibody.
*p-value for comparing patients with clinical remission and patients without clinical remission at week 30; †p<0.05.

60 of 98 patients (61.2%) received original infliximab achieved clinical remission at week 54 (p=0.555). Drug switching occurred at week 30 in the switching groups (CT-P13-infliximab group and infliximab-CT-P13 group). Study arm (CT-P13-CT-P13, CT-P13-infliximab, infliximab-CT-P13, and infliximab-infliximab) was not associated with clinical remission at week 54 in univariable logistic regression analysis (Supplementary Tables 2 and 3).

Concomitant immunomodulator use (OR, 2.236; 95% CI, 1.157 to 4.322; p=0.017), baseline CDAI score (OR, 0.993; 95% CI, 0.987 to 0.999; p=0.029) and infliximab trough level >4.5 μg/mL at week 6 (OR, 4.698; 95% CI, 2.279 to 9.685; p<0.001) were independently related to clinical remission at week 54 in multivariable analysis (Supplementary Table 2). A combined ROC analysis using infliximab trough level at week 6, baseline CDAI, and concomitant immunomodulator use revealed an AUC of 0.748 (95% CI, 0.676 to 0.820). Clinical remission at week 14 (OR, 4.377; 95% CI, 2.052 to 9.339; p<0.001), normal CRP level (<5 mg/L) at week 14 (OR, 2.266; 95% CI, 1.064 to 4.825; p=0.034), and infliximab trough level >4.0 μg/mL at week 14 (OR, 13.099; 95% CI, 3.626 to 47.317; p<0.001) were independently related to clinical remission at week 54 (Supplementary Table 3). A combined ROC analysis using infliximab trough level >4.0 μg/mL at week 14, clinical remission at week 14, and normal CRP levels at week 14 revealed an AUC of 0.825 (95% CI, 0.764 to 0.885) (Fig. 2B).

Serum infliximab concentration threshold of 3 μg/mL at week 6 reached clinical remission rates at week 54 greater than 60% (Fig. 3B). Serum infliximab concentration threshold of 3 μg/mL at week 14 reached clinical remission rates at week 54 greater than 75%, suggesting that serum infliximab level at week 14 may serve as a more useful predicting factor for clinical remission rate than that of week 6 (Fig. 3E).

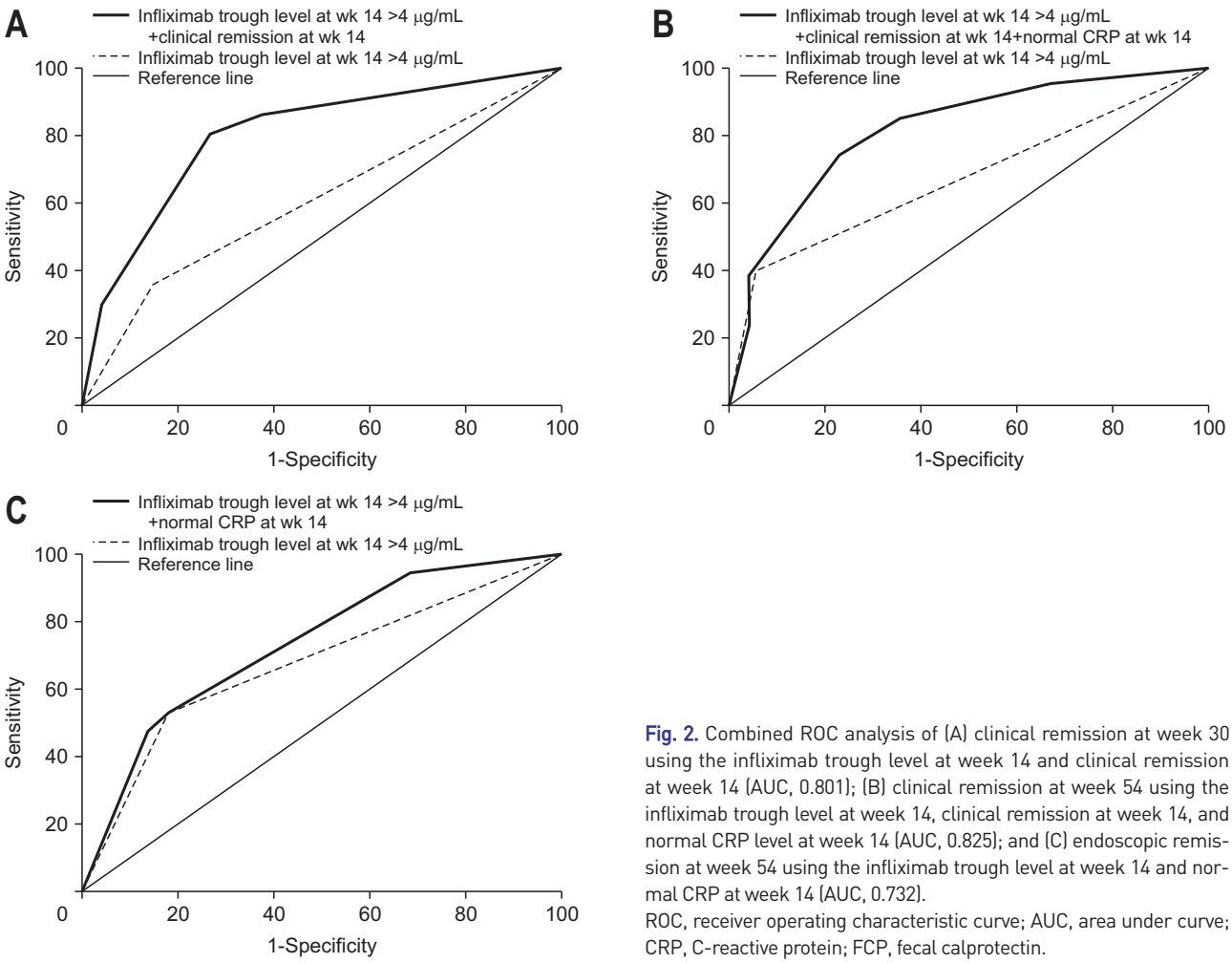

Fig. 2. Combined ROC analysis of (A) clinical remission at week 30 using the infliximab trough level at week 14 and clinical remission at week 14 (AUC, 0.801); (B) clinical remission at week 54 using the infliximab trough level at week 14, clinical remission at week 14, and normal CRP level at week 14 (AUC, 0.825); and (C) endoscopic remission at week 54 using the infliximab trough level at week 14 and normal CRP at week 14 (AUC, 0.732).
ROC, receiver operating characteristic curve; AUC, area under curve; CRP, C-reactive protein; FCP, fecal calprotectin.

4. Association of biochemical factors and early infliximab trough levels with endoscopic remission at week 54

Study arm (CT-P13-CT-P13, CT-P13-infliximab, infliximab-CT-P13, and infliximab-infliximab) was not associated with endoscopic remission at week 54 (Supplementary Tables 4 and 5).

Concomitant immunomodulator use (OR, 2.224; 95% CI, 1.124 to 4.404; p=0.022), infliximab trough level >4.5 μg/mL at week 6 (OR, 3.367; 95% CI, 1.651 to 6.464, p<0.001) were positively associated with endoscopic remission at week 54 (Supplementary Table 4). A combined ROC analysis using infliximab trough level at week 6 and concomitant immunomodulator use revealed an AUC of 0.691 (95% CI, 0.605 to 0.776). In multivariable analysis, normal CRP level (<5 mg/L) at week 14 (OR, 2.992; 95% CI, 1.124 to 7.969; p=0.028) and infliximab trough level >4 μg/mL at week 14 (OR, 4.312; 95% CI, 2.093 to 8.885; p<0.001) were positively associated with endoscopic remission at week 54 (Supplementary Table 5). A combined ROC analysis using infliximab trough level >4 μg/mL at week 14 and normal CRP levels at week 14 revealed an AUC of 0.732 (95% CI, 0.654 to 0.810) (Fig. 2C).

Serum infliximab concentration threshold of 9 μg/mL at week 6 reached endoscopic remission rates at week 54 greater than 30% (Fig. 3C). Serum infliximab concentration threshold of 7 μg/mL at week 14 reached endoscopic remission rates at week 54 greater than 50%, suggesting that serum infliximab level at week 14 may serve as a more useful predicting factor for endoscopic remission rate than that of week 6 (Fig. 3F).

DISCUSSION

Our *post hoc* analysis is the first study to compare serum infliximab trough levels and immunogenicity between original infliximab and CT-P13 groups in biologic naïve patients with CD. We demonstrated that there were no significant differences in serum infliximab trough levels and ADA levels between the groups. After adjustment of confounders, including concomitant immunomodulator,

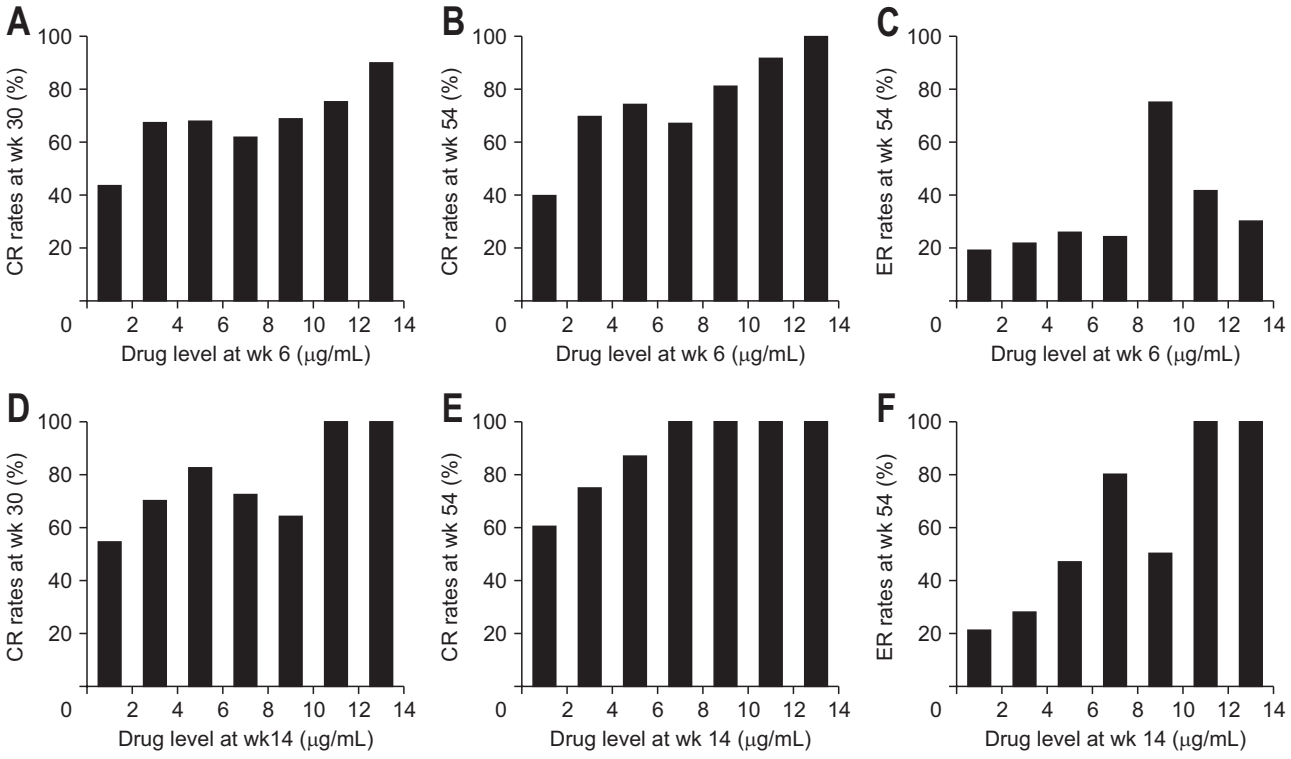

Fig. 3. Clinical outcomes according to the drug serum concentrations. (A) Clinical remission (CR) rates at week 30, (B) CR rates at week 54, and (C) endoscopic remission (ER) rates at week 54 in relation to the drug serum levels at week 6. (D) CR rates at week 30, (E) CR rates at week 54, and (F) ER rates at week 54 in relation to the drug serum levels at week 14.

ADA, and study arm, both serum trough levels greater than 4.5 μg/mL at week 6 and serum trough levels greater than 4 μg/mL at week 14 were independently associated with clinical remission at week 30, clinical remission at week 54, and endoscopic remission at week 54.

Our study has an implication on clinical usefulness of serum infliximab trough level in predicting treatment responses of both CT-P13 and originator infliximab. Bortlik *et al.*[20] showed that serum infliximab trough level >3 μg/mL at weeks 14 to 22 predicted a sustained clinical response in CD patients treated with originator infliximab. Singh *et al.*[21] found an association between serum infliximab trough level >3, >4, and >7 μg/mL at week 14 and clinical remission rate of 64%, 76%, and 100%, at week 54, respectively, in CD patients treated with originator infliximab. Cornillie *et al.*[22] carried out a *post hoc* analysis of ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) I trial. The serum infliximab trough level ≥4.5 μg/mL at week 14 and ≥60% CRP decrease were related to durable sustained response through week 54 in patients treated with originator infliximab. In terms of CT-P13, Gonczi *et al.*[15] suggested serum infliximab trough level ≥16.9 μg/mL at week 2 was associated with clinical response at week 14 in patients with CD treated with CT-P13. However, serum infliximab levels at weeks 14 and 30 were not associated with the long-term clinical outcomes at weeks 30 and 54. Moreover, endoscopic remission was not assessed.[15] The difference of cutoffs could be affected by various factors including therapeutic drug monitoring assay type and definition of therapeutic outcomes. We propose the cutoff serum infliximab trough level >4.5 μg/mL at week 6 and >4.0 μg/mL at week 14 for clinical remission at weeks 30 and 54, which is similar cutoff compared to those of previous studies with originator infliximab. Furthermore, we demonstrated that higher serum infliximab trough levels at weeks 6 or 14 could predict the endoscopic remission at week 54.

The efficacy and safety of CT-P13 compared to originator infliximab were demonstrated to be comparable in various previous studies.[3,14,16,23] However, there were few studies that compared serum infliximab trough levels of two drugs. Schulze *et al.*[24] investigated serum infliximab trough levels and ADA levels at weeks 2, 6, 14, 22, 30, and 38 for IBD patients treated with CT-P13 (n=33) and originator infliximab (n=86). Although the sample size was small and patients with previous use of an anti-TNF-α agent (42.0%) were included, serum infliximab concentration in both groups measured identical levels over 38 weeks.[24] Martínez-Feito *et al.*[18] also assessed serum infliximab trough levels and ADA levels at weeks 2, 6, 14, and 22 for IBD patients treated with CT-P13 (n=42) and originator inflix-

imab (n=44). In contrast to the previous study conducted by Schulze *et al.*,[24] serum infliximab trough levels at weeks 2, 6, 14, and 22 were lower in CT-P13 group compared to originator infliximab group.[18] There were some limitations to conclude these results because of their retrospective design, patients from the two different cohorts, small sample size, inclusion of previous use of biological therapy (22.1%), and a larger proportion of isolated colonic CD in originator infliximab group (18% vs 3%, p=0.09). The strength of our study is that it prospectively compared the infliximab trough levels between the two groups with a relatively large sample size, and demonstrated a long-term predictive role of early infliximab trough levels for clinical remission as well as endoscopic remission.

In our study, dose escalation up to 10 mg/kg was performed in only 12 patients (CT-P13 group, seven patients; originator infliximab group, five patients) after week 22. Of the 12 patients who experienced dose intensification, 10 patients (CT-P13 group, five patients [71.4%]; originator infliximab group, five patients [100%]) did not achieve early infliximab trough level 4.0 μg/mL at week 14. This suggests that performing infliximab dose intensification with less than 4.0 μg/mL serum infliximab trough levels at week 14 might have benefited from optimizing the dose of infliximab.

We performed the combinations of clinical remission at induction period or CRP normalization with early infliximab trough level, which improved the prediction of long-term clinical or endoscopic remission. The normalization of CRP levels was confirmed to be an important monitoring parameter in CD treatment with infliximab.[20,25,26] Recently, initiative of the International Organization for the Study of Inflammatory Bowel Disease recommended a treat to target strategy for IBD patients including clinical remission, normalization of CRP, and fecal calprotectin in updated Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II.[27] Correspondingly, our study suggests that combination of proactively assessed serum infliximab level after infliximab induction therapy could contribute to optimizing and personalizing CD treatment with CT-P13 or original infliximab.

In terms of the ADA positivity, there was no difference between CT-P13 group and originator infliximab group. The ADA positivity at week 14 was not associated with long-term clinical remission and endoscopic remission in multivariate analysis. Nevertheless, the importance of measurement of ADA levels in clinical practice should not be overlooked. In our results, although statistically not significant in multivariate logistic analysis, the ADA positivity at week 14 was negatively associated with clinical remission at week 54 in univariate logistic analysis (OR, 0.468; 95% CI, 0.222 to 0.990; p=0.047) (Supplementary Table 3). The relationship between ADA positivity and clinical outcomes is still conflicting in the previous studies.[20,28-30] Baert *et al.*[31] suggested that ADA concentration ≥8.0 μg/mL could predict short term clinical outcomes in CD patients treated with originator infliximab. The quantifying ADA levels might improve the possible correlation between clinical outcomes and ADA levels.

We demonstrated that concomitant immunomodulator was positively associated with the clinical remission at week 54, as seen in SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) trial and ACCENT 1 trial.[22,32] The ADA positivity rate at week 14 was lower in patients with immunomodulator compared to those without immunomodulator (9.4% vs 24.8%, p=0.005). Also, concomitant immunomodulator was negatively associated with the ADA positivity at week 14 in univariate logistic analysis (OR, 0.314; 95% CI, 0.138 to 0.715; p=0.006; data are not shown). Interestingly, the early serum infliximab trough levels were not different between those with or without immunomodulator use. Although the impact of immunomodulator on serum infliximab trough levels and ADA levels were conflicting, combination therapy with infliximab and immunomodulator could improve the clinical outcome in CD patients.[20,21]

The limitation of our study was the involvement of switching groups between originator infliximab and CT-P13 after week 30. Although clinical remission at week 30 was not affected by switching group, clinical remission and endoscopic remission at week 54 could be affected by switching between drugs. Nevertheless, we conducted adjustment of study arm for all multivariable logistic regression analysis and the study arm was not associated with clinical and endoscopic outcomes. Also, we investigated ADA positivity/negativity status rather than quantifying ADA levels, which could be more useful when interpreting data. This study is a *post hoc* analysis of the previous CT-P13 3.4 study (NCT02096861), which is an international, randomized, double-blind, phase 3 study in CD patients. We were not able to obtain the data on the Montreal classification of CD. Therefore, we could not assess the association between CD phenotypes and target trough levels in terms of clinical remission.

In conclusion, serum infliximab trough levels and ADA levels are comparable in biologic naïve CD patients treated with CT-P13 compared to originator infliximab. Serum infliximab trough levels at weeks 6 and 14 could predict clinical remission at weeks 30 and 54 and endoscopic remission at week 54. In addition, the combinations of clinical remission, fecal calprotectin normalization, or CRP normalization with early infliximab trough level could

greatly improve the prediction of long-term clinical or endoscopic remission.

CONFLICTS OF INTEREST

J.H.C. reports personal fees from Celltrion, Eisai Korea, Ferring Korea, Janssen Korea, Pfizer Korea, and Takeda Korea outside the submitted work. K.M.L. reports personal fees from Celltrion, Abbvie Korea, Ferring Korea, Janssen Korea, Pfizer Korea, and Takeda Korea outside the submitted work. Y.H.K. reports personal fees from Celltrion, Chong Kun Dang Pharmaceutical Co., Daewoong Pharmaceutical Co., Eisai Korea, Ferring Korea, Ildong Pharmaceutical Co., Janssen Korea, Pfizer Korea, Sama Pharm Co., Takeda Korea, and Whan In Pharm outside the submitted work. B.D.Y. has served on advisory boards for AbbVie Korea, Celltrion, Daewoong Pharma, Ferring Korea, Janssen Korea, Pfizer Korea, and Takeda Korea; has received research grants from Celltrion and Pfizer Korea; has received consulting fees from Chong Kun Dang Pharm., CJ Red BIO, Cornerstones Health, Daewoong Pharma, IQVIA, Kangstem Biotech, Korea United Pharm. Inc., Medtronic Korea, NanoEntek, and Takeda; and has received speaking fees from AbbVie Korea, Celltrion, Ferring Korea, IQVIA, Janssen Korea, Pfizer Korea, Takeda, and Takeda Korea. S.H.K., S.H.L., and J.H.L. are employees of, and have stocks for, Celltrion. S.S. reports personal fees from Abbvie, personal fees from Arena, personal fees from BMS, personal fees from Biogen, personal fees from Celltrion, personal fees from Celgene, personal fees from IMAB, personal fees from Gilead, personal fees from MSD, personal fees from Mylan, personal fees from Pfizer, personal fees from Fresenius, personal fees from Janssen, personal fees from Takeda, personal fees from Theravance, personal fees from Provention Bio Inc., personal fees from Protagonist, personal fees from Falk, outside the submitted work. J.P. and C.S.E. have no conflict of interest.

J.H.C. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.H.C., K.M.L. Data acquisition: J.P., J.H.C., K.M.L., Y.H.K., B.D.Y., C.S.E., S.S. Data analysis and interpretation: J.P., J.H.C., K.M.L. Drafting of the manuscript: J.P., J.H.C. Critical revision of the manuscript for important intellectual content: J.H.C., K.M.L., Y.H.K., B.D.Y., C.S.E. Statistical analysis: J.P., J.H.C. Administrative, technical, or material support: S.H.K., S.H.L., J.H.L. Study supervision: K.M.L. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220005.

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