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Original Article

Real-world safety and efficacy of CT-P13, an infliximab biosimilar, in Japanese rheumatoid arthritis patients naïve to or switched from biologics

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ABSTRACT

Objectives: The aim of this post-marketing surveillance (PMS) study is to evaluate the real-world safety and efficacy of CT-P13, the first biosimilar of infliximab (IFX).

Methods: Japanese patients with rheumatoid arthritis were prospectively registered from November 2014 and followed up for 1 year.

Results: Of 794 patients in the analysis set, 318 patients naïve to biological disease-modifying antirheumatic drugs (bDMARDs) showed an immediate decrease in Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP) and increased remission rate (DAS28-CRP < 2.6). In patients who switched from IFX to CT-P13 for non-medical reasons ($n = 374$), the low DAS28-CRP due to previous IFX treatment decreased further with continued CT-P13 therapy. As in naïve patients, patients who switched from other bDMARDs, mainly for medical reasons ($n = 102$), responded similarly to CT-P13. CT-P13 in this PMS and IFX in a previous PMS had similar adverse reaction profiles, although the incidence rate in naïve patients in this current PMS was lower due to earlier initiation of CT-P13 therapy.

Conclusions: CT-P13 showed excellent effectiveness as first-line therapy, no clinical difficulties in switching from IFX, and clinical improvement in patients who failed other bDMARDs. CT-P13 could be a cost-effective alternative to IFX in the treatment of rheumatoid arthritis.

KEYWORDS: CT-P13; infliximab biosimilar; Post-marketing surveillance; rheumatoid arthritis

Introduction

Infliximab (IFX) is a chimeric monoclonal antibody to tumour necrosis factor-α (TNFα) and approved for the treatment of various inflammatory diseases including rheumatoid arthritis (RA). CT-P13 is the first biosimilar of IFX having an identical amino acid sequence and a comparable higher-order structure. After the expiration of patents and the data exclusivity period for the originator IFX, CT-P13 was developed for socioeconomic reasons. For its regulatory approval, randomized studies comparing CT-P13 with the originator IFX were conducted in patients with RA and ankylosing spondylitis, and clinical comparability to the originator IFX was demonstrated with respect to pharmacokinetics, adverse drug reaction (ADR) profile, and efficacy for those diseases [1, 2]. After the approval, two randomized controlled studies demonstrated that CT-P13 had a non-inferior efficacy and a similar frequency of ADRs to the originator IFX [3, 4]. In Japan, CT-P13 was approved based on similar results in comparative Phase 1/2 studies with Japanese RA patients [5, 6]. However, those clinical trials were conducted in a limited number of patients in a specially selected homogenous subpopulation. For example, the trials excluded patients who had had previous therapy with biological disease-modifying antirheumatic drugs (bDMARDs).

In 2014, we initiated a large-scale post-marketing surveillance (PMS) of a variety of Japanese patients treated with CT-P13 in real-world settings [7, 8]. In this prospective PMS, we firstly intended to analyse the safety and efficacy of CT-P13 in a large number of bDMARDs-naïve patients to confirm the clinical outcome observed in the Japanese clinical trials. The safety profile was also to be compared with previous PMS data of the originator IFX. Secondly, we examined whether switching to CT-P13 from IFX is acceptable in terms of safety and maintaining clinical effectiveness.

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Thirdly, we explored the clinical effect of CT-P13 in patients who switched from previous treatment with other bDMARDs due to inadequate response or adverse events (AEs). In addition, we analysed the association of patients' characteristics and RA-related medication with the safety and efficacy of CT-P13.

Materials and methods

Post-marketing surveillance

Nippon Kayaku Co., Ltd. (Tokyo, Japan) initiated PMS in patients with RA after approval of CT-P13 in Japan. Patients were enrolled prospectively from November 2014 for 6 years and followed up for 1 year. The target number for analysis was 1000 patients who had been treated with CT-P13 for at least 4 months. This sample size provides a power of 95% or more to detect one patient experiencing an ADR at an incidence of 0.3%, which corresponds to the reported incidence of tuberculosis in the PMS of the originator IFX [9]. Patients were defined as those with RA not successfully treated with other conventional therapies who received treatment with CT-P13 according to the Japan College of Rheumatology guideline for TNF inhibitor use in RA. Information on prior treatment of RA and use of concomitant medications with CT-P13 were collected. The CT-P13 regimen was recorded, and changes in scheduled dosage and dosing interval were reported with the reasons for those changes. Case report forms (CRFs) were collected from each patient 4 months and 1 year after the start of treatment.

The PMS was required by the Ministry of Health, Labour and Welfare (MHLW) as a condition for the approval of CT-P13. It was conducted according to the continuous prospective surveillance method in order to minimize patient selection bias using a centralized registration system. The protocol and ethical considerations of the PMS study (Code IFX11) were assessed by internal review board members and approved by the MHLW, and no additional formal ethics committee approval was needed. The PMS was conducted in accordance with the Good Post-marketing Study Practice Ordinance of the MHLW, and informed consent from individual patients was not required.

Safety

All AEs including subjective/objective findings and laboratory test data were collected, and the causal relationship of AEs to the study drug, CT-P13, was evaluated. AEs and ADRs, for which a causal relationship with CT-P13 was not ruled out, were coded in accordance with the System Organ Class and Preferred Term listed in the Medical Dictionary for Regulatory Activities (MedDRA/J; version 20.0). ADRs of particular interest were infusion reaction (IR), serious infections (including tuberculosis), interstitial lung disease, and malignant neoplasms.

Efficacy

Patients underwent a baseline disease status assessment, including Disease Activity Score in 28 joints (DAS28). Efficacy of CT-P13 was evaluated by using DAS28 with C-reactive protein (DAS28-CRP). Cut-off values for high, moderate, and low disease activities were 5.1, 3.2, and 2.6, respectively, and remission was defined as DAS28-CRP < 2.6. The European League Against Rheumatism (EULAR) response criteria, with cut-off decreases in DAS28 of 0.6 and 1.2, were also applied for the evaluation of CT-P13. Efficacy was also evaluated by changes in DAS28 with erythrocyte sedimentation rate (DAS28-ESR) with the same cut-off values of 5.1, 3.2, and 2.6 [10, 11].

The data obtained on the nearest day to the scheduled administration time points (on weeks 2 and 6 and every 8 weeks thereafter for naïve patients to IFX and every 8 weeks for patients who switched from IFX to CT-P13) were used as the representative values.

Statistical analysis

Persistence of CT-P13 was plotted using the Kaplan–Meier method, with treatment discontinuation as an event. Patients who discontinued treatment within 7 days after the start of treatment were excluded from the plots. Differences between patient groups were analysed using the log-rank test.

Univariate analysis followed by multivariable analysis were performed using a logistic regression model to explore the risk factors for the occurrence of IRs, serious infections, and other ADRs. The logistic model was also applied for efficacy analysis to find baseline predictive factors associated with disease remission (DAS28-CRP < 2.6) between 14/16 and 30/32 weeks after the CT-P13 administration. As explanatory categorized variables, eight patient background factors (sex, age, disease duration, Steinbrocker stage and class, rheumatoid factor, CRP values, and history of drug allergy) and four therapeutic factors [prior bDMARDs, concomitant use of steroid and conventional synthetic DMARDs (csDMARDs), and dosage of methotrexate (MTX)] were used. Sex and age were forced into the multivariable logistic model, and the remaining patient factors were selected by the stepwise method. The odds ratio (OR) and its two-sided Wald 95% confidence interval (95% CI) were estimated for each covariate. *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

In this prospective PMS of CT-P13, 1004 patients were registered, and CRFs were not yet available for 199 patients as of July 2020. Of the 805 patients whose CRFs had been collected after 4 months of treatment, 526 patients had been followed up for 1 year. Eleven patients were excluded from this interim analysis, and a total of 794 were included in the safety analysis set. Evaluable DAS28-CRP data were missing from 100 patients, and 694 patients were included in the efficacy analysis set (Figure 1).

The use of bDMARDs prior to PMS entry was utilized to classify patients into three groups: (1) 318 patients who were naïve to bDMARDs and treated with CT-P13 as the first biological therapy; (2) 374 patients who had been treated with the originator IFX and switched to CT-P13 for non-medical reasons such as reduction of drug cost burden and hospital policy, and (3) 102 patients who had received other bDMARDs and switched to CT-P13 for mainly medical reasons such as AEs and inadequate response. Prior bDMARDs to CT-P13 included four TNF inhibitors [golimumab ($n = 22$), etanercept ($n = 21$), adalimumab ($n = 7$), and certolizumab pegol ($n = 7$)] and two non-TNF inhibitors [tocilizumab ($n = 27$) and abatacept ($n = 18$)].

The representative patient characteristics, disease status, and concomitant medications in each group are summarized

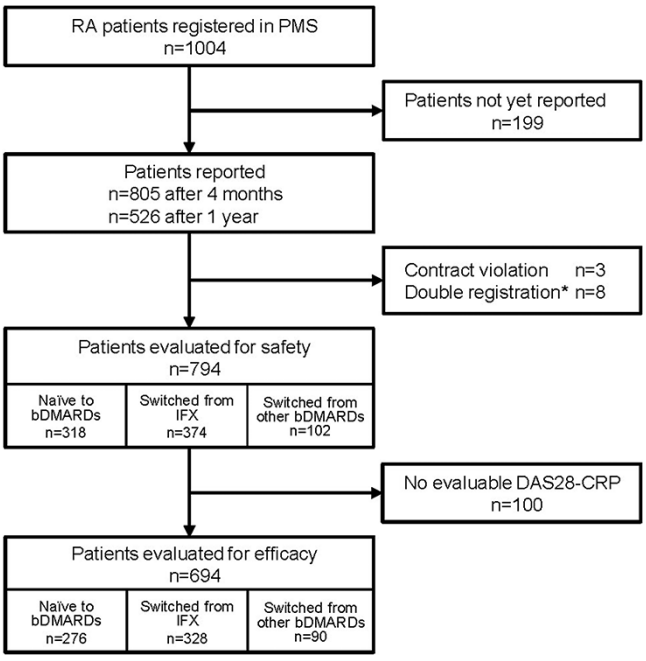

Figure 1. Patient disposition.

*Reregistration due to hospital transfer.
bDMARDs: biological disease-modifying antirheumatic drugs; DAS28-CRP: Disease Activity Score in 28 joints with C-reactive protein; IFX: infliximab; PMS: post-marketing surveillance; RA: rheumatoid arthritis.

in Table 1. About three-quarters of the patients in each group were female, and the average age in each group was almost the same, around 60 years old. However, the average disease duration was shorter in naïve patients (5.2 years) than in patients in the two switched groups (13.7 and 12.1 years), and the comorbidities rate was lower. The proportions of patients in the advanced Steinbrocker stages III/IV and functional classes III/IV, which are useful classical measures for comparing recent PMS data of CT-P13 with historical PMS data of IFX [12], were also low in the naïve patient group (29.9% and 17.3%, respectively). Among these three groups, patients who switched from IFX had less severe disease and their concomitant use of a steroid or csDMARDs was infrequent. However, the average dosage of CT-P13 used for the patients who switched from IFX (4.6 mg/kg/day) was higher than that used for the other two groups of patients (3.8 mg/kg), who were naïve to CT-P13 and IFX. The initial dose of CT-P13 after switching from IFX was the previous IFX dosage, which might have increased during the course of previous treatment to reach stable disease status. MTX was added to the treatment regimen in almost all patients as indicated by the approved directions for use. The baseline dosage of MTX used in naïve patients (10.0 mg/week) was higher than that used in switched patients. While 89.8% of patients who switched from IFX had been treated with IFX as the first biological therapy, 39.2% of patients who switched from other bDMARDs had experienced treatment failure with at least two previous bDMARDs. Additional patient details can be found in Table S1 in Supplemental Materials.

Incidence of adverse drug reactions

Among the 794 patients in the safety analysis set with observation period of 608.62 patient-years, 262 ADRs were reported in 185 patients (23.3%, 30.4 per 100 patient-years), and 46

Table 1. Characteristics and disease status of patients with rheumatoid arthritis treated with CT-P13 in PMS.

Parameters	Naïve to bDMARDs ($n=318$)	Switched from IFX ($n=374$)	Switched from other bDMARDs ($n=102$)	Total ($n=794$)
Patient characteristics				
Female rate (%)	73.3	78.3	77.5	76.2
Age (years)	56.8 ± 13.3	60.7 ± 13.2	59.9 ± 14.7	59.0 ± 13.6
Disease duration (years)	5.2 ± 7.2	13.7 ± 9.7	12.1 ± 10.4	10.0 ± 9.7
Body weight (kg)	56.0 ± 11.1	55.7 ± 11.2	56.0 ± 11.8	55.9 ± 11.3
Comorbidities (%)	49.1	60.2	54.9	55.0
Disease status				
Steinbrocker stage III + IV (%)	29.9	53.6	55.7	44.3
Steinbrocker functional class III + IV (%)	17.3	14.7	30.2	17.7
CRP (mg/dL)	1.9 ± 2.5	0.5 ± 1.1	1.5 ± 2.2	1.1 ± 2.0
ESR (mm/h)	41.3 ± 28.6	26.3 ± 19.4	33.3 ± 26.9	32.7 ± 25.1
DAS28-CRP	4.10 ± 1.27	2.26 ± 1.02	3.88 ± 1.42	3.12 ± 1.47
DAS28-ESR	4.71 ± 1.35	2.96 ± 1.10	4.33 ± 1.39	3.76 ± 1.48
Medication				
CT-P13 dose (mg/kg/day)	3.8 ± 0.9	4.6 ± 1.9	3.8 ± 1.0	4.2 ± 1.5
Steroid use (%)	52.1	31.0	47.1	41.5
csDMARDs use (%)[a]	34.4	13.4	27.5	23.6
MTX use (%)	99.4	98.7	93.1	98.2
MTX dose (mg/week)	10.0 ± 3.2	7.5 ± 3.1	8.3 ± 3.9	8.6 ± 3.4
Previous bDMARDs used (%)				
None	100.0	–	–	40.1
1 drug	–	89.8	60.8	50.1
≥2 drugs	–	10.2	39.2	9.8

Values are expressed as % or mean ± standard deviation.
bDMARDs: biological disease-modifying antirheumatic drugs; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; IFX: infliximab; MTX: methotrexate; PMS: post-marketing surveillance.
[a]csDMARDs include tacrolimus, mizoribine, bucillamine, leflunomide, salazosulfapyridine, and iguratimod but not MTX.

Table 2. Incidence of ADRs and serious ADRs to CT-P13 in 794 patients in safety analysis set during the observation period of 608.62 patient-years.

Number of patients Observed patient-years	Naïve to bDMARDs $n = 318$ 218.08		Switched from IFX $n = 374$ 328.61		Switched from other bDMARDs $n = 102$ 61.92		Total $n = 794$ 608.62	
	ADRs	SADRs	ADRs	SADRs	ADRs	SADRs	ADRs	SADRs
Number of reported ADRs	127	16	83	17	52	13	262	46
Number of patients with ADRs	89	15	59	14	37	10	185	39
Incidence of ADRs per number of patients (%)	28.0	4.7	15.8	3.7	36.3	9.8	23.3	4.9
Incidence rate of ADRs per 100 patient-years	40.8	6.9	18.0	4.3	59.8	16.1	30.4	6.4
Category of ADRs classified by SOC (occurred in ≥3 patients in total)								
Blood and lymphatic system disorders	3 (0.9%)	–	1 (0.3%)	–	1 (1.0%)	–	5 (0.6%)	–
Gastrointestinal disorders	5 (1.6%)	–	6 (1.6%)	2 (0.5%)	1 (1.0%)	–	12 (1.5%)	2 (0.3%)
General disorders and administration site conditions	4 (1.3%)	1 (0.3%)	3 (0.8%)	2 (0.5%)	2 (2.0%)	–	9 (1.1%)	3 (0.4%)
Hepatobiliary disorders	9 (2.8%)	–	5 (1.3%)	1 (0.3%)	1 (1.0%)	–	15 (1.9%)	1 (0.1%)
Infections and infestations	27 (8.5%)	7 (2.2%)	22 (5.9%)	9 (2.4%)	10 (9.8%)	3 (2.9%)	59 (7.4%)	19 (2.4%)
Injury, poisoning, and procedural complications	24 (7.6%)	2 (0.6%)	14 (3.7%)	1 (0.3%)	15 (14.7%)	3 (2.9%)	53 (6.7%)	6 (0.8%)
Investigations	12 (3.8%)	–	3 (0.8%)	–	5 (4.9%)	1 (1.0%)	20 (2.5%)	1 (0.1%)
Metabolism and nutrition disorders	1 (0.3%)	–	–	–	2 (2.0%)	–	3 (0.4%)	–
Musculoskeletal and connective tissue disorders	5 (1.6%)	1 (0.3%)	2 (0.5%)	–	–	–	7 (0.9%)	1 (0.1%)
Neoplasms benign, malignant, and unspecified	1 (0.3%)	1 (0.3%)	1 (0.3%)	–	1 (1.0%)	1 (1.0%)	3 (0.4%)	2 (0.3%)
Nervous system disorders	5 (1.6%)	2 (0.6%)	5 (1.3%)	–	2 (2.0%)	1 (1.0%)	12 (1.5%)	3 (0.4%)
Renal and urinary disorders	–	–	2 (0.5%)	–	2 (2.0%)	–	4 (0.5%)	–
Respiratory, thoracic, and mediastinal disorders	11 (3.5%)	1 (0.3%)	8 (2.1%)	2 (0.5%)	3 (2.9%)	3 (2.9%)	22 (2.8%)	6 (0.8%)
Skin and subcutaneous tissue disorders	4 (1.3%)	–	6 (1.6%)	–	2 (2.0%)	–	12 (1.5%)	–
ADRs of particular interest								
Infusion reactions	24 (7.6%)	2 (0.6%)	14 (3.7%)	1 (0.3%)	15 (14.7%)	3 (2.9%)	53 (6.7%)	6 (0.8%)
Infections with serious cases	11 (3.4%)	7 (2.2%)	11 (3.0%)	9 (2.4%)	6 (5.9%)	3 (2.9%)	28 (3.6%)	19 (2.4%)
Tuberculosis (Tuberculous peritonitis)	1 (0.3%)	1 (0.3%)	–	–	–	–	1 (0.1%)	1 (0.1%)
Bacterial pneumonia[a]	5 (1.6%)	3 (0.9%)	4 (1.1%)	4 (1.1%)	5 (4.9%)	3 (2.9%)	14 (1.8%)	10 (1.3%)
Pneumocystis jirovecii pneumonia	1 (0.3%)	1 (0.3%)	–	–	–	–	1 (0.1%)	1 (0.1%)
Herpes zoster	3 (0.9%)	1 (0.3%)	5 (1.3%)	3 (0.8%)	1 (1.0%)	–	9 (1.1%)	4 (0.5%)
Cellulitis	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	–	–	2 (0.3%)	2 (0.3%)
Endocarditis	–	–	1 (0.3%)	1 (0.3%)	–	–	1 (0.1%)	1 (0.1%)
Interstitial lung disease	3 (0.9%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (2.9%)	3 (2.9%)	7 (0.9%)	5 (0.6%)
Malignant neoplasms[b]	1 (0.3%)	1 (0.3%)	1 (0.3%)	–	1 (1.0%)	1 (1.0%)	3 (0.4%)	2 (0.3%)

Data are expressed as the number (%) of patients with ADRs.
ADRs: adverse drug reactions; bDMARDs: biological disease-modifying antirheumatic drugs; IFX: infliximab; SADRs: serious adverse drug reactions; SOC: system organ class.
[a]Bacterial pneumonia includes pneumonia, pneumonia bacterial, and pneumonia pneumococcal.
[b]Reported malignant neoplasms were gastric cancer, lymphoproliferative disorder, and carcinoid tumour of the stomach.

serious ADRs were reported in 39 patients (4.9% and 6.4) (Table 2). In the naïve patients, ADRs and serious ADRs were observed at 28.0% and 4.7%, respectively. As compared with naïve patients, patients who switched from IFX had a lower incidence (15.8% and 3.7%) and patients who switched from other bDMARDs had a higher incidence (36.3% and 9.8%). IRs were the most frequent ADRs, especially in patients who switched from other bDMARDs. Infection was commonly observed, and bacterial pneumonia ($n = 14$) and herpes zoster ($n = 9$) were reported in ≥1% of patients. Tuberculous peritonitis was reported in one male naïve patient after five doses of CT-P13, although he had no tuberculosis history and no signs of tuberculosis on prior chest radiography. Reported ADRs of particular interest also included interstitial lung disease ($n = 7$) and malignant neoplasms ($n = 3$). The types of ADRs observed with CT-P13 were similar to those reported with the originator.

AEs and serious AEs were observed in 254 patients (32.0%, 41.7 per 100 patient-years) and 55 patients (6.9% and 9.4), respectively. All reported AEs classified by the System Organ Class are listed in Table S2.

Risk factors for adverse drug reactions

Univariate and multivariable logistic regression analyses were performed for IRs, serious infections, and other systemic ADRs separately since the characteristics and onset time after administration of these ADRs were different (Table S3 and Table 3). Prior bDMARDs treatment was a significant factor for IRs and other ADRs but not for serious infection. The incidence of IRs was significantly lower in patients who switched from IFX than in naïve patients, and significantly higher in patients who switched from other bDMARDs than in naïve patients. No factor other than prior bDMARDs was significantly associated with IR, but history of drug allergy had a high OR (1.96, 95% CI: 0.85–4.52, $P = 0.116$). Older age (≥65 years) was significantly associated with the occurrence of serious infection (OR = 3.24, 95% CI: 1.38–7.60, $P = 0.007$). For other ADRs, female sex and concomitant use of steroids were risk factors (OR = 0.45, 95% CI: 0.27–0.78, $P = 0.004$; OR = 1.66, 95% CI: 1.12–2.47, $P = 0.012$). No significant association of ADRs was detected with the use of csDMARDs or higher dosages of MTX (>10 mg/week).

Efficacy

The mean DAS28-CRP of naïve patients decreased rapidly from 4.10 at baseline to 2.87 at week 2 and then gradually dropped to 2.26 and 2.13 at weeks 30 and 54 after the administration of CT-P13, respectively (Figure 2(a)). The baseline score (3.88) of patients who switched from other bDMARDs decreased similarly to 2.49 and 2.29 at week 32 and week 56, respectively. However, the decrease in the score was smaller than that obtained in naïve patients. In contrast, the DAS28-CRP of patients who switched from IFX was already 2.26 before starting CT-P13 and decreased further to around 2.0.

The proportion of patients responding to CT-P13 increased during the treatment period (Figure 2(b,c)). After the treatment with CT-P13 for 30 weeks, 69% of naïve patients achieved remission (DAS28-CRP < 2.6), and 75% showed a good or moderate response. Patients switched from other bDMARDs showed a comparable remission rate (69%) and

Table 3. Multivariable logistic regression analysis of baseline factors associated with incidence of infusion reactions, serious infections, and other ADRs ($n = 793$).

Baseline factor	Category (reference)	n	Infusion reactions		Serious infections		Other ADRs	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex	Male	188	0.66 (0.31–1.39)	0.269	1.49 (0.64–3.44)	0.354	0.45 (0.27–0.78)	0.004**
	Female (reference)	605						
Age (years)	≥65	314	0.64 (0.34–1.21)	0.171	3.24 (1.38–7.60)	0.007**	1.04 (0.69–1.57)	0.850
	<65 (reference)	479						
History of drug allergy	Yes	69	1.96 (0.85–4.52)	0.116	0.86 (0.19–3.85)	0.842	1.03 (0.51–2.07)	0.941
	No (reference)	724						
Steroid use	Yes	329	1.03 (0.58–1.85)	0.919	1.91 (0.84–4.31)	0.122	1.66 (1.12–2.47)	0.012*
	No (reference)	464						
csDMARD use	Yes	187	0.95 (0.49–1.84)	0.884	0.68 (0.25–1.86)	0.449	1.42 (0.92–2.19)	0.115
	No (reference)	606						
MTX dosage (mg/week)	>10	230	0.92 (0.48–1.76)	0.801	1.57 (0.64–3.87)	0.327	1.10 (0.70–1.72)	0.681
	≤10 (reference)	563						
Prior bDMARDs (patient group)	Switched from other bDMARDs	102	1.98 (0.96–4.07)	<0.001***	1.99 (0.67–5.90)	0.178	1.20 (0.68–2.12)	0.132
	Switched from IFX	374	0.44 (0.21–0.92)	<0.001***	1.06 (0.41–2.78)	0.514	0.64 (0.40–1.02)	0.017*
	Naïve (reference)	317						

*$P < 0.05$,
**$P < 0.01$,
***$P < 0.001$.
ADRs: adverse drug reactions; bDMARDs: biological disease-modifying antirheumatic drugs; CI: confidence interval; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; IFX: infliximab; MTX: methotrexate; OR: odds ratio.

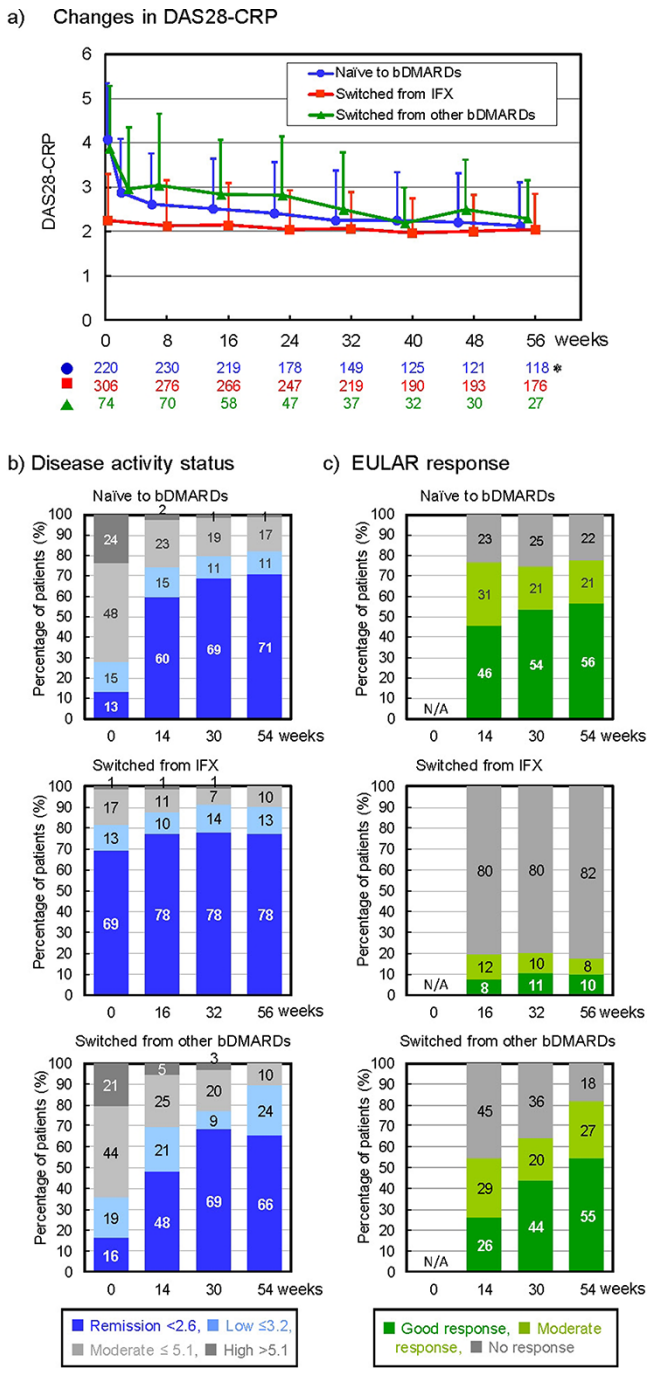

Figure 2. Efficacy of CT-P13 based on DAS28-CRP. (a) Changes in DAS28-CRP (mean ± SD) over time from baseline to week 56, (b) distribution of patients by disease activity status, and (c) distribution of patients who achieved a EULAR response.

*Number of analysed patients with DAS28-CRP values at each time point. bDMARDs: biological disease-modifying antirheumatic drugs; DAS28-CRP: Disease Activity Score in 28 joints with C-reactive protein; EULAR: European League Against Rheumatism; IFX: infliximab; N/A: not applicable.

a response rate (64%) at week 30. In contrast, remission had been obtained in 69% of patients who switched from IFX at the start of CT-P13 therapy due to the prior treatment with the originator IFX. The remission rate reached 78% with further treatment with CT-P13. Consequently, the response rate was not high because baseline DAS28-CRP had already dropped due to the pretreatment with IFX, which limited the possibility of its further decrease. Similar response patterns to CT-P13 were observed when DAS28-ESR was used as an efficacy parameter (Figure S1a, b, and c).

Factors associated with disease remission

In multivariable logistic regression analysis of efficacy, a significant association of the Steinbrocker functional class (OR = 0.36, 95% CI: 0.21–0.64, $P < 0.001$) and baseline CRP (OR = 0.31, 95% CI: 0.19–0.51, $P < 0.001$) with the achievement of disease remission by treatment with CT-P13 was observed (Figure 3). The number of previously used bDMARDs was also found to affect the odds of achieving remission. In a polytomous analysis, previous use of two or more bDMARDs, compared to no previous use, was associated with lower OR of achieving disease remission (OR = 0.37, 95% CI: 0.16–0.84, $P = 0.007$), while the use of one bDMARD was a favourable factor for remission (OR = 1.10, 95% CI: 0.64–1.89, $P = 0.028$), since 84% of the patients were switched from IFX for non-medical reasons. Concomitant use of steroid and csDMARDs, and dosage of MTX were not significantly associated with the achievement of remission in multivariable analysis, although those were significant risk factors in univariate analysis (Table S4). The remission rates by background factors are presented in Supplemental Materials (Figure S2a, b, and c).

Treatment persistence and reasons for drug discontinuation

The Kaplan–Meier curves showed significantly higher treatment persistence in patients who switched from IFX compared to the other two patient groups ($P < 0.001$), and 84% of the patients were on CT-P13 therapy at week 56 (Figure 4). The treatment persistence rate of the naïve patients decreased to 52% at week 56. The patients who switched from other bDMARDs showed the shortest treatment duration of CT-P13, although no statistically significant difference in treatment duration was shown between patients who switched from other bDMARDs and naïve patients ($P = 0.17$, log-rank test).

A total of 271 patients (34.1%) discontinued CT-P13 treatment during the PMS period. The common reasons for discontinuation were insufficient efficacy ($n = 102$, 12.8% of total patients), ADRs ($n = 72$, 9.1%), and patient decision ($n = 32$, 4.0%). Among them, 18 patients were switched to the originator IFX. Treatment was discontinued after remission in 20 patients (2.5%) (Table S5).

During the PMS period, the dose of CT-P13 was modified in 65 of 794 patients (8.2%) to overcome inadequate efficacy with the initial dose regimen. The dose was escalated in 56 patients (1.5 times or more), and the dosing interval was shortened in 9 patients (from 8 to 6 weeks or less). In patients who switched from IFX, for whom efficacy was generally maintained, dose or schedule modifications were made in only 8 patients (2.1%) (Table S6). Of the 65 patients requiring the intensive treatment, 35 patients (53.8%) continued CT-P13 therapy, even though they failed to respond to the initial regimen. The discontinuation rate due to insufficient efficacy was 29.2%, and no withdrawal after remission was obtained. AEs leading to drug discontinuation did not increase and

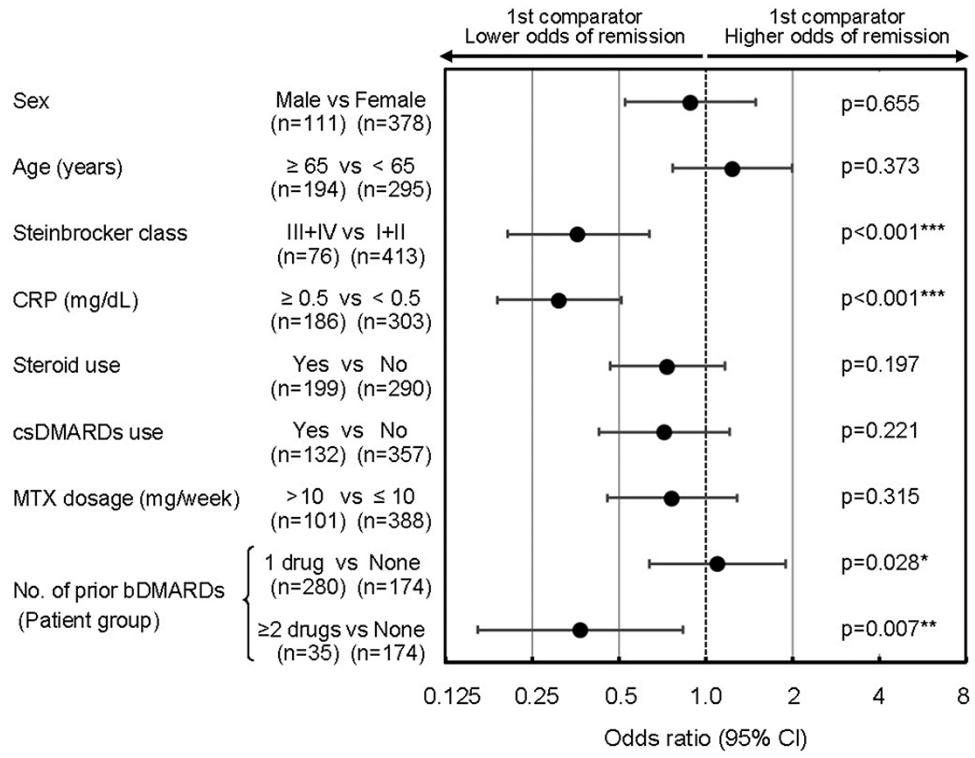

Figure 3. Multivariable logistic regression analysis of baseline factors associated with disease remission (DAS28-CRP <2.6) observed between 14/16 and 30/32 weeks after the CT-P13 administration.

bDMARDs: biological disease-modifying antirheumatic drugs; CI: confidence interval; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

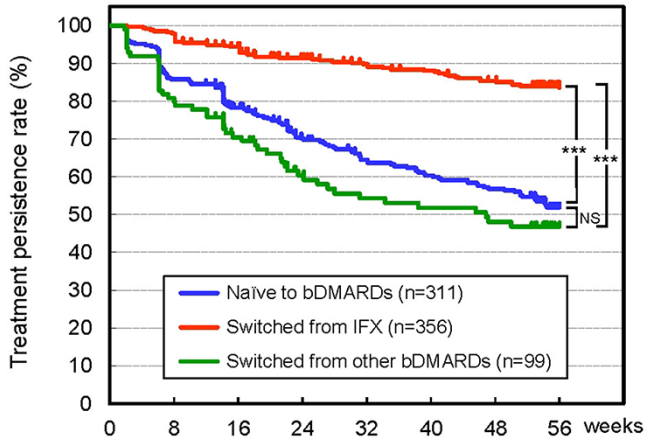

Figure 4. Kaplan–Meier plot of persistence of CT-P13 treatment. Patients who ceased further treatment with CT-P13 earlier than 7 days from the initial administration were excluded from the plot. Statistical significance was analysed by the log-rank test.

bDMARDs: biological disease-modifying antirheumatic drugs; IFX: infliximab; NS: not significant.
***$P < 0.001$.

were 6.2% with the intensive dose regimen of CT-P13 (Table S7).

Discussion

In this, the first report on the PMS of CT-P13 in Japanese patients with RA, we analysed the incidence of adverse reactions, efficacy outcome with DAS28-CRP, and treatment continuation rate by Kaplan–Meier analysis. A widely varying population of 794 patients was divided into three groups according to prior bDMARD use: patients who were naïve to treatment with bDMARDs, patients who switched from originator IFX, and patients who switched from other bDMARDs. The treatment with CT-P13 was considered 'biological induction therapy' in the naïve patient group, 'maintenance therapy' in the stable patient group treated with IFX, and 'altered therapy' in the group of patients experiencing treatment failure with other bDMARDs. Accordingly, the disease status in each group was quite different.

In the first group of naïve patients, the incidence of ADRs was 28.0%, which was the same as the previously reported incidence of 28.0% for IFX in PMS [9]. However, the observation period in the former PMS was set to 6 months, while that in our PMS was 1 year. Therefore, the rate of ADRs per 100 patient-years was lower in the CT-P13 population than that in the IFX population (40.8 vs 59.4). Counting only ADRs occurring within 6 months, the incidence of ADRs of CT-P13 decreased from 28.0% to 19.2% (50.4 per 100 patient-years). The incidence of serious ADRs was also lower with CT-P13 (4.7%, 6.9 per 100 patient-years) than with IFX (6.2%, 13.1). The reason for the lower incidence of ADRs of the naïve patients in this PMS might be the less severe disease status due to the early initiation of CT-P13 therapy. In fact, the disease duration in naïve patients was short (5.2 years vs 9.9 years in the IFX PMS), and the proportion of patients in advanced Steinbrocker stages III/IV and class III/IV were low (29.9% vs 71.5%; 17.3% vs 36.1%, respectively)

(Table 1 and [9]). This is the result of a paradigm shift in therapeutic strategies that use bDMARDs from the early stages of RA [13–16]. The profile of ADRs observed with CT-P13 was similar to that reported in IFX-treated patients, and no new safety signals were detected. The most common ADRs were IRs and infections. Special attention should be paid to tuberculosis, since the incidence of tuberculosis in Japan is still not low [17]. Extensive investigation showed that an increased risk of tuberculosis with anti-TNF therapy is related to the local prevalence of latent tuberculosis but not disease type, age, or sex [18–20]. The tuberculosis burden in Japan is intermediate, and 14 tuberculosis cases (0.28%) were reported in 5000 Japanese patients with RA in the PMS of IFX [9]. Among them, 11 cases occurred in the first 2000 patients just after the introduction of IFX, but the incidence was reduced to 3 per the remaining 3000 patients (0.10%) because of appropriate guidelines for examination and prophylactic drug use. In this PMS, even though a prior chest radiograph or gamma interferon releasing assay was performed in all patients, one naïve patient (0.13%) developed tuberculosis. Continuous careful inspection should be required. The response to CT-P13 was excellent in naïve patients. DAS28-CRP decreased 1.84 points from 4.10 to 2.26 at week 30, and 75% of patients achieved good or moderate response according to the EULAR criteria. This efficacy was comparable to the Japanese clinical trial, where CT-P13 and IFX reduced the baseline DAS28-CRP values (5.19 and 5.30) by 2.08 and 1.96 at week 30 and achieved good or moderate response in 82% and 80% of patients, respectively [5]. Thus, comparable efficacy of CT-P13 to IFX in a first-line treatment shown in clinical trials was confirmed in naïve patients in this PMS. Furthermore, the remission rate (DAS28-CRP <2.6) was also high, such as 71% at 54 weeks (Figure 2(b)). This cut-off value for DAS28-CRP, which is used in many global studies with IFX and CT-P13, has been reported to underestimate disease activity in Japanese RA patients compared to the original DAS28-ESR <2.6, and a lower cut-off for remission <2.3 was proposed [21, 22]. Even with this cut-off value, the remission rate was as high as 65%, and remission rate accessed with DAS28-ESR <2.6 was 53% (Figure S1b). This remission rate is higher than those reported previously with IFX [21, 23, 24], probably because CT-P13 was used from an early non-progressive stage of disease according to recent treatment guidelines [15, 16, 25]. In addition, recently approved dose intensifications (i.e. dose escalation and shortened dosing interval) may contribute to the high remission rate. In fact, the dose of CT-P13 was modified in 42 naïve patients (13.2%) in this PMS, and 23 patients (54.8%) succeeded to continue CT-P13 therapy even though they failed to respond to the ordinal regimen. Even with intensive treatment with CT-P13, discontinuation due to AE occurred only in 2 cases (4.8%) (Tables S6 and S7). In contrast to the remission rate, the rate of CT-P13 continuation in the first year in naïve patients was 55%, which was lower than the previously reported rate with IFX [23, 26]. Recent reports have revealed that the retention rate of bDMARDs has declined over time, and increased available treatment options have lowered the hurdle for patients to switch/discontinue treatment with biologics [25, 27]. Aggressive changes of treatment to achieve disease remission according to the treat-to-target strategy may also contribute to lower drug continuation rates [13, 14].

No clinical difficulties were associated with switching from IFX to CT-P13 in this PMS, as reported previously [3, 28, 29]. The disease activity in this second patient group was generally controlled by previous treatment with the originator IFX. At the start of CT-P13, DAS28-CRP was already 2.26, and 69% of patients had reached remission. This effectiveness due to previous IFX was similar to that observed in naïve patients 30 weeks after the start of CT-P13 treatment. Continued administration of CT-P13 as maintenance therapy further decreased DAS28-CRP and increased remission rate (Figure 2). The incidences of ADRs and serious ADRs were low (15.8% and 3.7%, respectively). Consequently, the rate of treatment continuation was as high as 84% even after 1 year (Figure 4). The number of patients who discontinued treatment due to ADRs and insufficient efficacy was only 20 (5.3%) and 22 (5.9%), respectively, but 14 patients (3.7%) decided to discontinue treatment (Table S5). This is an example of the so-called 'nocebo effect', which is a characteristical problem associated with the use of biosimilars [30]. Furthermore, in this group of patients who switched from IFX, 11 patients discontinued CT-P13 to switch back to IFX, despite the much lower drug price of CT-P13 than IFX. In Japan, the National Health Insurance drug price of biosimilars is set at 70% of the price of the originator at the time of approval, and then further decreased through periodical price revision reflecting the market drug price. Clinical data showing the equivalence of the biosimilar with its originator as described in this report must be provided to overcome the nocebo effect as well as to show the cost-effectiveness of the biosimilar.

The third group of patients who switched from other bDMARDs had a long disease duration and complex treatment history of prior bDMARDs. The baseline DAS28-CRP was as high as that in naïve patients and significantly decreased after the start of CT-P13. The decrease was smaller compared to the naïve group (−1.39 at 32 weeks vs −1.84 at 30 weeks), but remission and good response were obtained at a similar rate to the naïve group. The higher the number of prior bDMARDs, the lower the remission rate (Figure S2c). The remission rate of patients who switched from non-TNF inhibitors (48.2%, $n=27$) was lower than that of patients who switched from other TNF inhibitors (60.0%, $n=35$), although significance was not shown due to the small number of patients (Table S4). Based on the treat-to-target paradigm, switching bDMARDs has been common practice in patients who have an inadequate response to previous bDMARDs. Therefore, these efficacious results could be a practical basis for switching to CT-P13 after treatment failure with other bDMARDs. The incidence of ADRs in this patient group (36.3%) was higher than those in other patient groups, and discontinuation due to ADRs was observed in 17 patients (16.7%). Thus, the persistence of CT-P13 therapy after 1 year was 47%, which was lower than the rate of 55% in naïve patients ($P=0.17$) (Figure 4).

In multivariable logistic regression analyses of baseline factors, prior therapy status was a significant factor affecting the efficacy and safety of CT-P13 (Figure 3, Table 3). In addition, Steinbrocker functional class and baseline CRP level were significantly associated with lower odds of remission. Previous studies have reported that these factors were significant predictors of IFX efficacy, consistent with our results [21, 23]. The incidence of IR was significantly lower in patients who

switched from IFX than in naïve patients (3.7% vs 7.6%, $P < 0.001$). This might be due to a kind of channelling bias stemming from this study's exclusion of patients who discontinued IFX because of IR to IFX. On the contrary, the incidence of IR was higher in patients previously treated with other bDMARDs than in naïve patients (14.7% vs 7.6%, $P < 0.001$). This might be due to the higher rate of patients with history of drug allergy in this patient group (14.7% vs 3.5%, $P < 0.001$). History of drug allergy showed higher OR (1.96) for association with IR in the multivariable analysis, but no statistical significance was obtained ($P = 0.116$) since patients who switched from IFX were included in the analysis. However, in the previously reported PMS of CT-P13 in patients with inflammatory bowel disease, a significant association of history of drug allergy with IR was demonstrated [7]. Older age (≥65 years) was a risk factor for serious infections with the use of CT-P13. This finding corresponded to the reported results of IFX use [9, 31, 32]. For general ADRs other than IRs and serious infections, female sex and steroid use were risk factors. The dosage of MTX has been increasing after approval of high doses up to 16 mg/week in Japan [15], but no significant association of MTX dosage with ADRs or efficacy was indicated by multivariate analysis in this PMS (Table 3, Figure 3). In clinical practice, high-dose MTX must be carefully administered, followed by gradual tapering to maintain efficacy while controlling ADRs.

There are limitations in this study. First, as compared with clinical trial data, collected data of this PMS were inherently sparse and reporting items were limited. However, the real-world information obtained in a large variety of patients must be useful in the clinical treatment of RA. Second, this PMS was a single-arm study of CT-P13, so it was not designed to be compared with the originator IFX directly. We attempted to compare our data with historical data from previous clinical trials and the PMS of IFX, but a simple comparison could not be made due to changes in the patient background with recent advances in RA therapy. However, we could collect updated data in recent practical treatment systems and novel information on switching treatment from previously treated bDMARDs including originator IFX.

Overall, in this interim analysis of prospective PMS, CT-P13 exhibited sufficient efficacy in naïve patients. In patients who switched from IFX, the efficacy of previously administered IFX was maintained, and the period of treatment continuation was extended. Even in switched patients who failed to respond to other bDMARDs, CT-P13 showed similar efficacy to that observed in naïve patients. No new safety signal was added to those of the originator IFX. Therefore, CT-P13 could be a cost-effective alternative to IFX in the treatment of patients with RA.

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Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

T.T. has received grants from AbbVie, Asahi Kasei Pharma, Ayumi Pharmaceutical, Boehringer-Ingelheim, Chugai Pharmaceutical, Daiichi Sankyo, DNA Chip Research, Eisai, Eli Lilly Japan, Mitsubishi Tanabe Pharma, Nippon Kayaku, Ono Pharmaceutical, and UCB Japan; consultancy fees from AbbVie, Astellas Pharma, Chugai Pharmaceutical, Eli Lilly Japan, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, and Pfizer Japan; and speaker fees from AbbVie, Ayumi Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly Japan, Gilead Sciences, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, Pfizer Japan, Sanofi, and UCB Japan. K.N. was, and FY is, an employee of Nippon Kayaku. S.O. has received speaker or consulting fees from AbbVie, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, and Takeda Pharmaceutical. M.I. has no conflict of interest to disclose. Y.Y. has received speaker fees from Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Mitsubishi Tanabe Pharma, and Ono Pharmaceutical. H.Y. has received speaker or consultant fees from Teijin Pharma and YL Biologics.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, took responsibility for the integrity of the work as a whole, and have given their approval for publication.

Data availability

The data sets generated during the current study are available from Nippon Kayaku on reasonable request.

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