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Post-marketing analysis for biosimilar CT-P13 in inflammatory bowel disease compared with external data of originator infliximab in Japan

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Key words
CT-P13, database search, IBD, infliximab biosimilar, post-marketing surveillance.

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Abstract

Background and Aim: CT-P13, an infliximab (IFX) biosimilar, was approved for treatment of inflammatory bowel disease. However, no comparison with the originator IFX in this indication has been conducted in Japan where endemic levels of tuberculosis and hepatitis virus infection are not low. We evaluated the safety and efficacy in real-world data of CT-P13 and compared with originator IFX data in Japan.

Methods: In a prospective post-marketing surveillance (PMS) study, patients who received CT-P13 in a 28-month period from January 2015 were followed up for 2 years. By conducting Japanese administrative database search (DBS) for the same period of PMS, data of the originator IFX including treatment persistence, tuberculosis incidence, and liver injury were analyzed retrospectively and compared with the corresponding PMS data of CT-P13.

Results: CT-P13 persistence in PMS (n = 640) and IFX persistence in DBS (n = 4113) were almost similar between patients who switched from the originator and patients who continued on the originator, and also between the biologics-naïve patient groups. There were no differences in the incidences of tuberculosis and hepatic injury (Tuberculosis: 2 patients [0.31%] with CT-P13, 10 patients [0.24%] with the originator, P = 0.75; Hepatic injury: 18.5% with CT-P13, 15.4% with the originator, P = 0.22). Most of the patients with hepatic injury continued treatment in PMS and DBS at similar rates (80.8% *vs* 83.6%, P = 0.65).

Conclusion: The results of long-term PMS of CT-P13 compared with external reference data from an administrative database suggested that the biosimilar and its originator were comparably useful in real-world clinical practice.

Declaration of conflict of interest: SS has served as a speaker for AbbVie, Takeda Pharmaceutical, Zeria Pharmaceutical; served as a consultant for Nippon Kayaku; and an endowed chair from AbbVie, EA Pharma, JIMRO, Kyorin Pharmaceutical, Mochida Pharmaceutical, and Zeria Pharmaceutical. KN was, and FY is, an employee of Nippon Kayaku. YS has received research funding from AbbVie, EA Pharma, JIMRO, Kissei Pharmaceutical, Mitsubishi Tanabe, Mochida Pharmaceutical, and Nippon Kayaku and served as a speaker for AbbVie, EA Pharma, Janssen, Kyorin Pharmaceutical, Mitsubishi Tanabe, Mochida Pharmaceutical, and Zeria Pharmaceutical. MW has received research funding from and served as a consultant for AbbVie, EA Pharma, Kissei Pharmaceutical, Mitsubishi Tanabe, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, and Zeria Pharmaceutical; received research funding from Kyorin Pharmaceutical and Miyarisan Pharmaceutical; and served as a consultant for Celltrion, Eli Lilly, Gilead Sciences, Janssen, and Nichi-Iko Pharmaceutical. TH has received research funding from AbbVie, EA Pharma, Otsuka Holdings, and Zeria Pharmaceutical and served as a speaker, a consultant, or an advisory board member for AbbVie, Aspen Japan, Ferring, Bristol Myers Squibb, Celltrion, EA Pharma, Eli Lilly, Gilead Sciences, Janssen, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Nichi-Iko Pharmaceutical, Mitsubishi Tanabe, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, and Zeria Pharmaceutical.

Author's contribution: YS, MW, and TH conceptualize the study. FY, YS, MW, and TH performed the investigation. SS, KN, and FY completed the methodology. KN and FY carried out the final analysis. FY validated the data. TH made the supervision. KN and FY made the visualization. SS, KN, and TH wrote the manuscript. All authors approved the final manuscript.

Ethical approval: The protocol of PMS study (Code IFX21) was submitted to and approved by the Ministry of Health, Labor and Welfare, and no formal ethics committee approval was needed. The retrospective DBS used information of anonymized patients, and no formal ethics committee approval was required, according to the Ethical Guidelines for Epidemiological Research issued by the Ministry of Health, Labor, and Welfare.

Informed consent: The PMS was conducted in accordance with the Good Post-marketing Study Practice Ordinance, and informed consent from individual patients was not required. The DBS used only anonymized patient data, and no informed consent from patients was needed.

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Introduction

CT-P13 is the first biosimilar of infliximab (IFX), an antitumor necrosis factor-α (TNFα) antibody used for the treatment of various inflammatory diseases. Both CT-P13 and the originator IFX are chimeric monoclonal antibodies and have an identical amino acid sequence and comparable higher order structure binding to TNFα. For its regulatory approval, comparative clinical studies with the originator IFX were conducted in patients with rheumatoid arthritis and ankylosing spondylitis, and approval for inflammatory bowel disease (IBD) was based on extrapolation of those data.[1,2] After the approval, two randomized controlled studies have demonstrated noninferior efficacy and similar frequency of adverse drug reactions (ADRs) of CT-P13 to the originator IFX.[3,4] In addition, accumulated results of observational clinical studies indicated similar safety profile, immunogenicity, and comparable efficacy in patients switched with CT-P13 from the originator IFX.[5–8]

The use of TNFα antagonists including IFX is associated with an increased risk of tuberculosis[9] and drug-induced liver injury.[10] The anti-TNF therapy is also known to reactivate latent tuberculosis and hepatitis B virus infections,[11] and the prevalence of tuberculosis infection and viral hepatitis in the Asia-Pacific region is much higher than in Western countries.[12–14] Higher risk of tuberculosis associated with originator IFX in Asian countries was well investigated,[15] but information on CT-P13-associated tuberculosis risk and hepatotoxicity in Asian patients with IBD is insufficient.[16] Therefore, it is especially important to explore the safety profile of CT-P13 including tuberculosis risk and hepatic injury in this region.

We initiated a large-scale post-marketing surveillance (PMS) of CT-P13 in Japanese patients with IBD and have reported its interim analysis of short-term safety and efficacy.[17] However, the PMS cohort is a single-arm prospective observational cohort of CT-P13 without originator IFX as comparator. In recent years, the development of administrative databases has led to database searches (DBS) for real-world information that can be applied to decision-making.[18] Even comparison of the results of a single-arm study with synthetic external control data from a database has been proposed especially for clinical studies where setting an appropriate control group is difficult for ethical or feasibility reasons, such as in rare disease studies and population-level health interventions.[19,20] We attempted to apply this concept to PMS of CT-P13. From the Japanese public insurance claims database, we retrieved administrative data of IBD patients prescribed IFX originator and compared these data to the corresponding updated PMS data of patients treated with CT-P13. Using these real-world data, long-term therapy persistence, tuberculosis incidence, and hepatic injury could be compared. In addition, we analyzed the association of demographic characteristics and IBD-related medication use with CT-P13 therapy persistence in PMS.

Methods

Post-marketing surveillance. Nippon Kayaku Co., Ltd. (Tokyo, Japan) initiated PMS in patients with Crohn's disease (CD) and ulcerative colitis (UC) after approval of CT-P13. Each patient was enrolled prospectively between January 2015 through April 2017 and followed up at 4 months, 1 year, and 2 years. Patient characteristics, disease status, CT-P13 regimen, previous therapy, concomitant medications, and ADRs during treatment including subjective/objective findings and laboratory test data were collected. Disease severity and steroid dependence/resistance are defined in the Japanese clinical practice guidelines for IBD[21] and the Japanese treatment guidelines for IBD,[22] respectively. Reported ADRs 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).

The protocol of PMS study (Code IFX21) was submitted to and approved by the Ministry of Health, Labor, and Welfare, and no formal ethics committee approval was needed. The PMS was conducted in accordance with the Good Post-marketing Study Practice Ordinance, and informed consent from individual patients was not required.

Database search. EBM Provider, an administrative database established by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan), was used.[23] In the database, the public health insurance claims data of about 30 million patients were collected from 397 hospitals in Japan. We investigated claims data of the patients who were diagnosed with IBD and were prescribed the originator IFX during the PMS period of CT-P13 (28 months from January 2015). The patients who were switched to CT-P13 were excluded. The database has compiled all claims data including diagnosis, drug prescription, medical practice, and examinations, but not results of examinations or laboratory tests. However, the laboratory test results were collected exclusively from approximately 10% of IBD patients from 38 hospitals. Direct description of ADRs or efficacy was not available.

The retrospective DBS used only information of anonymized patients and formal ethics committee approval or informed consent were not required, according to the Ethical Guidelines for Epidemiological Research issued by the Ministry of Health, Labor, and Welfare.

Outcomes

Persistence of infliximab treatment. Infliximab administration is indicated at 2 and 6 weeks after the first dose and then every 8 weeks. Therefore, discontinuation or withdrawal of treatment was determined when there was no prescription data for 85 days (1.5 times the dosing interval) or more despite the presence of a medical record. Patients without medical records were regarded as having transferred to another hospital or died and were treated as censored cases.

Tuberculosis. Possible cases of tuberculosis were retrieved by disease codes of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), and their records of prescription and examination were further examined. Tuberculosis onset was indicated by (i) medical record information (interferon-gamma release assay, diagnostic imaging, and/or bacteriological microscopic examination) within 4 weeks before and after the ICD-10 diagnosis and discontinuation of IFX prescriptions after diagnosis and (ii) new prescriptions of two or more antituberculosis drugs at the same hospital. The DBS for

tuberculosis history prior to originator IFX treatment extended back to 2008, when the database was established.

Drug-induced liver injury. The occurrence of drug-induced liver injury by IFX was examined based on changes in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels. In accordance with the Japan Society of Hepatology's diagnostic criteria, drug-induced liver injury was defined as ALT increased to more than twice the upper limit of normal (ULN), and ALP exceeding the ULN. In patients whose baseline levels were higher than the ULN, an increase in ALT or ALP during IFX treatment exceeding the ULN was used for the definition. The ULNs were defined the upper limits of reference ranges proposed by the Japanese Committee for Clinical Laboratory Standards. Specifically, the ULNs of ALT for male and female patients are 42 and 23 U/L, respectively, and the ULN of ALP is 322 U/L. Recovery of the elevated markers and persistence of IFX treatment (prescription within 85 days from the last day of elevated marker) were also investigated.

Statistical analysis. Persistence of CT-P13 in PMS and the originator IFX in DBS was plotted by the Kaplan–Meier method, with treatment discontinuation as an event. Patients who discontinued treatment within 7 days after the start of treatment and patients who switched from CT-P13 back to the originator IFX for the patient's or institutional reasons were excluded from the plots. Significant differences were analyzed using the log-rank test.

Univariate and multivariable analyses were performed using a Cox proportional hazard regression model to explore patient risk factors for CT-P13 persistence in PMS. From these analyses, medical switch patients who had complicated heterogeneous backgrounds were excluded for analytical reasons. CD and UC patients were separately analyzed. *P* values less than 0.05 were considered statistically significant.

Results

Patients in post-marketing surveillance and database search. In PMS, 700 patients were enrolled for CT-P13 treatment and followed for 2 years. As of July 2019, case report forms for 640 patients, consisting of 327 CD and 313 UC patients, were collected and analyzed (Fig. 1a). In addition to patients naïve to biologics before CT-P13, there were patients who switched from the originator IFX to CT-P13 for nonmedical reasons and patients who switched from the originator IFX or Adalimumab for medical reasons such as adverse events and loss of response. The representative patient characteristics and disease status in each group are summarized in Table 1. In these three groups, the proportion of patients with poor disease status and the rate of concomitant use of steroids and enteral nutrition were significantly lower in the nonmedical switch group.

We searched the health insurance claims database and detected 2600 CD and 1513 UC patients who were prescribed the originator IFX during the PMS period of CT-P13 (Fig. 1b). Much less information on patient demographics and disease conditions was available from the database than from PMS. Nevertheless, the age, male/female ratio, and rate of concomitant drug use in two patient groups (naïve patients and continued-treatment patients) in DBS were similar to those in the corresponding groups in PMS (naïve patients and nonmedical switch patients, respectively) (Table 1).

Treatment persistence

Comparison between post-marketing surveillance and database search. The persistence of CT-P13 treatment was higher in CD than in UC, as shown in Figure 2a (hazard ratio [HR] = 0.52, 95% confidence intervals [CI], 0.37–0.73, $P < 0.001$). The reason for discontinuation was shown in Table S1. Among the three patient groups, the nonmedical switch group showed the highest persistence rate in both CD and UC, indicating that CT-P13 maintained the efficacy of prior treatment with the originator IFX. The treatment persistence rate in patients switched for medical reasons was the lowest. These differences in the treatment persistence rate among the three patient groups (Fig. 2a) corresponded to the differences in disease severity and status in each group (Table 1).

The persistence of the originator IFX treatment according to the DBS was higher for naïve patients than continued-treatment patients who continued to take the originator IFX, in both CD and UC (Fig. 2b). The persistence curve of naïve patients receiving the originator IFX in DBS was remarkably similar to the persistence curve of naïve patients receiving CT-P13 in PMS. In fact, the 1-year persistence rates for CT-P13 and its originator were the same for both CD (84%) and UC (70%). Furthermore, the nonmedical switch group who switched from the originator IFX to CT-P13 in PMS and continued-treatment group who continued taking originator IFX in DBS showed similar treatment persistence curves.

Factors for CT-P13 persistence in post-marketing surveillance. In univariate analysis, prior therapy with the originator IFX was a significant factor associated with persistence of CT-P13 therapy, namely, nonmedical switch group had significantly low HR as compared with both naïve patients with CD and UC (Table 2), as is shown by Kaplan–Meier univariate analysis in Figure 2. Lower albumin (< 3.5 g/L) and higher C-reactive protein (CRP) level (≥ 0.5 mg/L) at baseline were associated with poor persistence of CT-P13, and more severe disease was a significant factor in UC. Another significant factor in CD patients was combination with steroid at baseline. No significant association was observed with age, sex, and smoking status in both CD and UC patients.

In multivariable Cox proportional hazard analysis, higher baseline CRP (HR = 3.45, 95% CI: 1.20–9.71, $P = 0.021$) and combination with steroid (HR = 2.57, 95% CI: 1.10–5.99, $P = 0.029$) in CD patients, and male (HR = 2.39, 95% CI; 1.24–4.61, $P = 0.009$) and combination with immunomodulators (HR = 0.52, 95% CI; 0.29–0.95, $P = 0.034$) in UC patients were identified as associated factors with persistence of CT-P13 in PMS.

Adverse drug reactions

Adverse drug reactions leading to discontinuation of CT-P13 in post-marketing surveillance. In the safety analysis set of 640 patients in PMS, ADRs caused by CT-P13 were

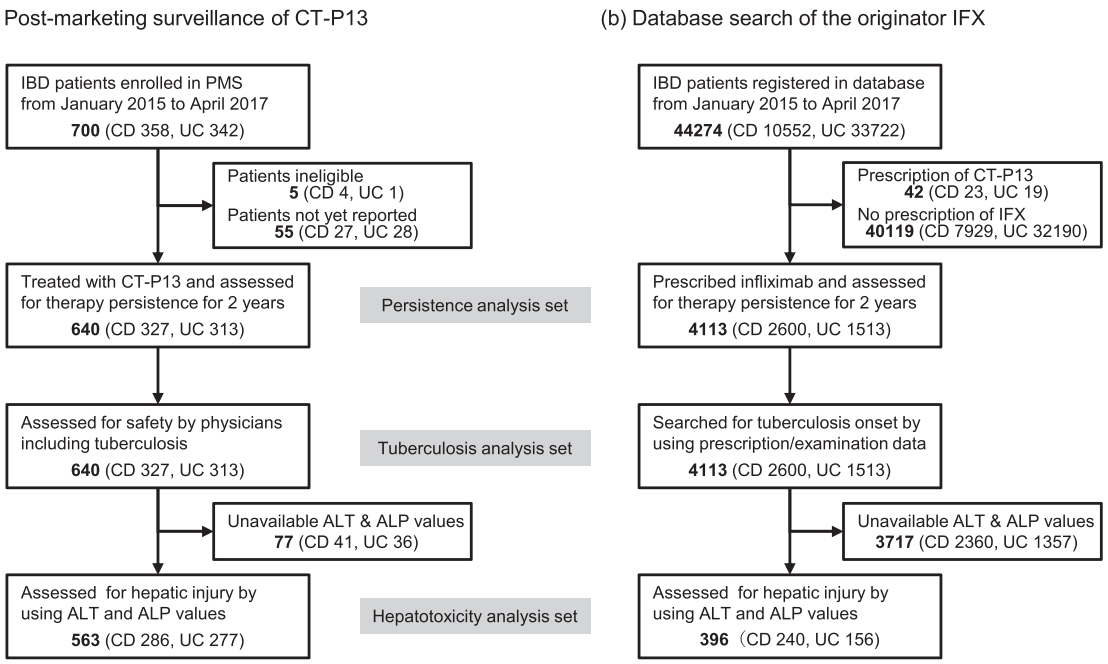

Figure 1 Flow diagrams showing the post-marketing surveillance (PMS) procedure for CT-P13 and database search (DBS) procedure for the originator infliximab (IFX). (a) PMS was designed to cover all Japanese patients with inflammatory bowel disease who received CT-P13 in a 28-month period from January 2015. Enrolled patients were followed up for 2 years, and case report forms collected until July 2019 were analyzed. Patients were stratified into three groups according to their history of prior biologics therapy. (b) DBS for inflammatory bowel disease patients who received the originator IFX was conducted during the same period as PMS. The retrieved health insurance claims data for 2 years of follow-up were analyzed in two patient groups: the biologics-naïve group and the continued-treatment group of patients who had been treated with the originator IFX.

reported in 157 patients, with an incidence of 24.5% (21.1 per 100 person-years). Of these patients, 62 (21 CD and 41 UC) discontinued CT-P13 therapy due to ADRs (Table S2). The incidences of ADRs in CD and UC patients were not significantly different.

The most common ADRs were infusion reactions, which occurred twice or more in some patients. Treatment was discontinued in 35 patients due to infusion reactions, accounting for more than half of the ADRs leading to discontinuation. Discontinuation was due to infection in six cases including two cases of tuberculosis, and hepatobiliary disorders in three CD patients and one UC patient with increase in hepatic markers such as ALT and bilirubin.

Tuberculosis: Comparison between post-marketing surveillance and database search. The results of PMS and DBS were compared for the onset of tuberculosis, an infectious disease requiring special attention because of its association with IFX treatment (Table 3). Tuberculosis was reported in 2 out of 640 patients (0.31%) treated with CT-P13 in PMS. Both patients were naïve to biologics. One male CD patient aged 61 years had no medical history, and all prior examinations for tuberculosis were negative, but tuberculous meningitis developed after seven doses of CT-P13. Another male patient with UC aged 61 years had a history of tuberculosis diagnosed at the age of 24 years (no treatment record available) but showed no abnormal imaging and was negative in the interferon-gamma release assay before CT-P13 administration. No antituberculosis drugs were used prophylactically, and tuberculosis was diagnosed after two doses of CT-P13.

In DBS, the onset of tuberculosis with originator IFX use was confirmed in 10 patients (0.24%) on the basis of diagnosis by ICD-10 coding, examinations before and after diagnosis, and subsequent discontinuation of IFX. The tuberculosis patients consisted of three naïve CD, three continued-treatment CD, three naïve UC, and one continued-treatment UC patient. Two out of the 10 patients were given new prescriptions of two or more antituberculosis drugs in the same hospital. Four patients had a history of tuberculosis treatment, and two patients had received isoniazid prophylactically. Chest imaging was examined prior to the IFX administration in all 10 patients, and interferon-gamma release assay or tuberculosis skin test was conducted in 7 of 10 patients.

There was no significant difference in the above incidences of tuberculosis between patients treated with CT-P13 and patients treated with the originator IFX ($P = 0.75$), and HR of tuberculosis onset was 1.70 (95% CI: 0.37–7.82, $P = 0.49$). Despite the initial negative tuberculosis screening in PMS and DBS, 12 out of 4753 patients (0.25%) developed tuberculosis in 2-year observation period.

Drug-induced liver injury: Comparison between post-marketing surveillance and database search. As shown in Table 4, evaluable sets of ALT and/or ALP values, as indicators for drug-induced liver injury, were obtained in 88% (563 patients) in PMS and only 9.6% (396 patients) in DBS. The incidences of

Table 1 Characteristics and disease status of patients with CD and UC treated with CT-P13 in PMS or the originator IFX in DBS

Parameters	CT-P13 in PMS (*n* = 640)						Originator IFX in DBS (*n* = 4113)			
	CD (*n* = 327)			UC (*n* = 313)			CD (*n* = 2600)		UC (*n* = 1513)	
	Naïve (*n* = 96)	Nonmedical switch (*n* = 174)	Medical switch (*n* = 57)	Naïve (*n* = 168)	Nonmedical switch (*n* = 93)	Medical switch (*n* = 52)	Naïve (*n* = 825)	Continued treatment (*n* = 1775)	Naïve (*n* = 783)	Continued treatment (*n* = 730)
Patient characteristics										
Female rate	27%	26%	30%	36%	33%	46%	31%	29%	41%	41%
Age (years)	33.6 ± 14.4	40.5 ± 14.6	36.3 ± 10.3	45.6 ± 15.6	43.2 ± 18.5	45.2 ± 15.2	34.9 ± 14.5	38.0 ± 12.3	41.6 ± 18.0	44.0 ± 15.4
Disease duration (years)	5.4 ± 8.0	11.5 ± 8.0	12.9 ± 8.1	7.4 ± 7.8	9.7 ± 8.9	8.5 ± 7.1	—	—	—	—
Body weight (kg)	57.0 ± 12.1	63.6 ± 12.3	59.2 ± 18.1	58.6 ± 11.7	61.2 ± 11.9	57.6 ± 11.4	—	—	—	—
BMI	20.7 ± 3.8	22.8 ± 3.9	21.2 ± 5.4	21.9 ± 3.7	22.4 ± 3.5	21.3 ± 3.5	—	—	—	—
Hospitalization	52%	9%	42%	59%	11%	62%	—	—	—	—
Current smoker	18%	13%	21%	6%	7%	2%	—	—	—	—
Past smoker	5%	10%	12%	13%	16%	19%	—	—	—	—
Disease severity and status										
Severe and moderate [†]	77%	51%	81%	95%	57%	90%	—	—	—	—
External fistula	19%	9%	9%	—	—	—	—	—	—	—
Anal lesion	46%	31%	51%	—	—	—	—	—	—	—
Steroid dependence [‡]	—	—	—	49%	40%	60%	—	—	—	—
Steroid resistance [‡]	—	—	—	36%	28%	17%	—	—	—	—
CRP (mg/L)	18 ± 24	3.7 ± 8.6	15 ± 21	20 ± 36	1.4 ± 2.3	18 ± 34	—	—	—	—
CDAI	191 ± 124	68 ± 69	178 ± 107	—	—	—	—	—	—	—
Partial Mayo score	—	—	—	5.6 ± 2.3	1.0 ± 1.9	5.0 ± 2.8	—	—	—	—
Concomitant drug use										
5-Aminosalicylic acid	91%	82%	74%	88%	87%	85%	79%	80%	87%	85%
Steroid	29%	17%	37%	55%	20%	60%	17%	12%	54%	22%
Azathioprine	29%	37%	49%	38%	33%	42%	29%	30%	38%	37%
Mercaptopurine	5%	4%	9%	10%	6%	4%	3%	5%	6%	7%
Enteral nutrition	64%	28%	39%	8%	2%	4%	55%	36%	16%	9%

Values are expressed as % or mean ± standard deviation.

[†]Severity is defined in Matsuoka et al.[21]

[‡]Steroid dependence and resistance are defined in Japanese treatment guidelines for inflammatory bowel disease.[22]

BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; DBS, database search; IFX, infliximab; PMS, post-marketing surveillance; —, data not available.

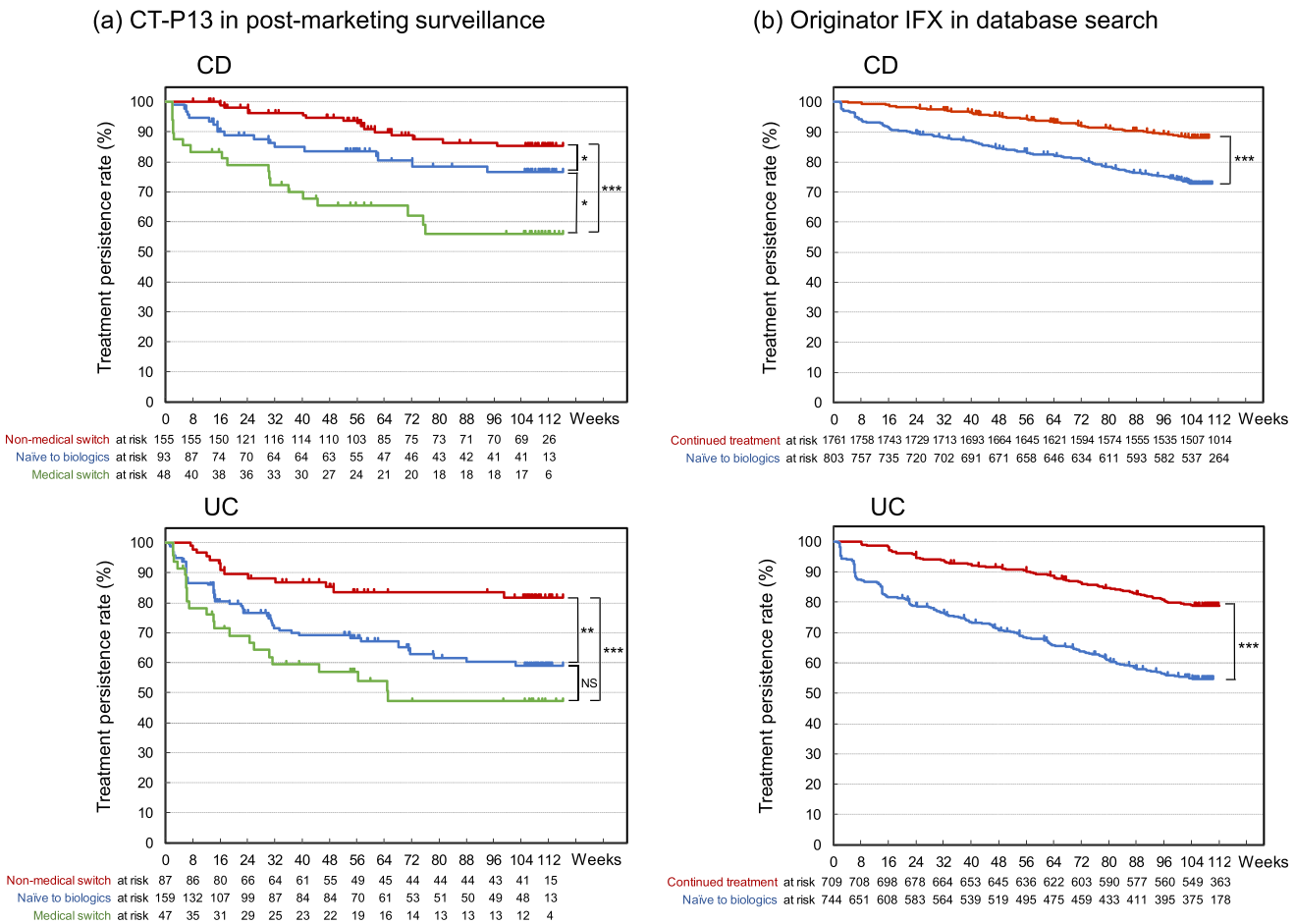

Figure 2 Kaplan–Meier plot of treatment persistence in patients with Crohn's disease (upper panels) and ulcerative colitis (lower panels). (a) Persistence with CT-P13 in post-marketing surveillance. ——, Naïve; – – –, Nonmedical switch; — —, Medical switch. (b) Persistence with the originator infliximab in database search. ——, Naïve; – – –, Continued treatment. Statistically significant differences were analyzed by the log-rank test. NS, not significant. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

elevated hepatic markers in patients treated with CT-P13 in PMS and the originator IFX in DBS were similar (18.5% and 15.4%, respectively) and not significantly different (odds ratio = 1.24, 95% CI: 0.88–1.76, $P = 0.22$). As with the rates of other ADRs, the rate of CT-P13-induced liver injury was low in the nonmedical switch group and corresponded to the rate of originator IFX-induced liver damage in the continued-treatment group, compared with naïve patient groups.

In the follow-up to the elevation of hepatic markers, administration of CT-P13 or the originator IFX could be continued in 80.8% and 83.6%, respectively, of patients with elevated ALT/ALP. The drug continuation rates were not significantly different (odds ratio = 1.21, 95% CI: 0.53–2.80, $P = 0.65$). In addition, it was confirmed that marker levels returned to the normal range in 79 patients (76.0%) in PMS, even though the treatment with CT-P13 was continued. Although 20 patients discontinued CT-P13 therapy after the elevation of ALT/ALP, only one patient discontinued it directly because of a hepatic disorder event, and the remaining patients discontinued treatment for other reasons.

Discussion

In this study, the long-term PMS data of CT-P13 in Japanese IBD patients were compared with data of its originator IFX retrieved from an administrative database during the same period. There was no significant difference between CT-P13 and the originator IFX in three clinical outcomes: treatment persistence rate, tuberculosis infection incidence, and onset of and recovery from hepatic injury.

Treatment persistence was mainly determined by efficacy (discontinuation due to remission, treatment change due to disease worsening) and occurrence of ADRs. Therefore, the similar treatment persistence observed for CT-P13 and the originator IFX suggests that the usefulness of both products is comparable in IBD patients in Japan.

Increased CRP and decreased albumin levels at baseline were significant factors associated with low CT-P13 therapy persistence in univariate analysis. High CRP and low albumin levels generally reflect severe disease status[24,25] and could cause discontinuation

Table 2 Univariate and multivariable Cox regression analysis of patient factors for persistence of CT-P13 therapy in CD and UC patients in PMS

Patient factor	Cut-off (Reference)	CD patients				UC patients			
		Univariate analysis		Multivariable analysis†		Univariate analysis		Multivariable analysis†	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prior biologics	Nonmedical switch (Reference: Naïve)	0.50 (0.26–0.99)	0.045*	1.69 (0.54–5.33)	0.368	0.40 (0.22–0.72)	0.002**	0.50 (0.21–1.15)	0.102
Age	Continuous variable	1.01 (0.98–1.03)	0.580	0.99 (0.96–1.02)	0.659	0.99 (0.98–1.01)	0.291	1.00 (0.98–1.01)	0.610
Sex	Male (Reference: Female)	0.89 (0.42–1.90)	0.762	0.53 (0.20–1.43)	0.212	1.35 (0.80–2.29)	0.256	2.39 (1.24–4.61)	0.009**
Smoking status	Current smoker (Reference: Never smoker)	1.06 (0.36–3.09)	0.920	1.52 (0.44–5.23)	0.510	0.23 (0.03–1.63)	0.140	0.18 (0.02–1.30)	0.088
	Past smoker (Reference: Never smoker)	2.20 (0.75–6.44)	0.151	3.03 (0.75–12.3)	0.121	0.83 (0.38–1.83)	0.648	0.73 (0.29–1.85)	0.510
Baseline albumin	< 3.5 g/dL (Reference: ≥ 3.5 g/dL)	2.42 (1.10–5.35)	0.029*	2.00 (0.70–5.75)	0.197	1.90 (1.12–3.23)	0.017*	1.46 (0.71–3.02)	0.308
Baseline CRP	≥ 5 mg/L (Reference: < 5 mg/L)	2.44 (1.20–5.05)	0.014*	3.45 (1.20–9.71)	0.021*	2.13 (1.30–3.48)	0.003**	1.18 (0.59–2.36)	0.635
Disease severity	Severe and moderate (Reference: Mild)	1.16 (0.57–2.37)	0.677	1.09 (0.40–2.98)	0.863	3.52 (1.41–8.76)	0.007**	2.16 (0.60–7.73)	0.237
Combination at baseline	With steroid (Reference: None)	2.43 (1.20–4.90)	0.014*	2.57 (1.10–5.99)	0.029*	1.51 (0.93–2.43)	0.094	1.13 (0.62–2.05)	0.690
	With immunomodulator (Reference: None)	0.96 (0.48–1.92)	0.910	0.72 (0.30–1.76)	0.472	0.92 (0.57–1.49)	0.721	0.52 (0.29–0.95)	0.034*

*$P < 0.05$,
**$P < 0.01$.
†Subject numbers for multivariable analysis of CD and UC patients were 191 and 178, respectively.
CI, confidence interval; HR, hazard ratio; PMS, post-marketing surveillance.

of CT-P13 therapy during the long treatment period. Previous pharmacokinetic studies reported that lower serum albumin increased clearance of IFX because it lowered protein binding and decreased the serum trough level of IFX.[26] Higher CRP was also reported to associate with induction of neutralizing antibody towards IFX.[27] The serum levels of IFX and neutralizing antidrug antibody were well-known critical parameters related to the clinical response to IFX. Steroid use at baseline was associated with poor persistence of CT-P13 therapy especially in CD patients. Steroid use often reflects severity of disease status, and a similar tendency with baseline CRP and albumin might be observed. The combination of immunomodulators with CT-P13 at baseline was a significant factor for treatment persistence in UC patients. The combination of IFX and immunomodulators is recommended for both CD and UC based on the results of randomized controlled trials such as SONIC[28] and UC-SUCCESS,[29] which showed beneficial effects and increase in serum concentration of IFX due to suppression of the induction of the neutralizing antibody. However, in these studies, immunomodulators were administered with IFX to patients who were naïve to both drugs, while in the PMS, immunomodulators had already been administered at the time of CT-P13 administration. In such a setting of treating CD patients with IFX in addition to immunomodulators, a meta-analysis and a cohort study showed no improved outcomes.[30,31] In contrast, in UC, significantly longer persistence of IFX treatment was reported when IFX was added to prior immunomodulators.[32] These different results in CD and UC patients correspond to the results of our analysis with real-world data.

The possible onset of tuberculosis was extracted first from searches based on ICD-10 codes and then by concomitant examination records and prescription data to exclude routine examinations or prophylactic use of antituberculosis drugs. An attempt to extract ADRs from the claims database by using disease codes alone was not always valid,[33] and this was the case for detection of tuberculosis infection. Onset of tuberculosis was detected in 10 out of 4113 patients prescribed the originator IFX (0.24%), but this number was not markedly different from the 2 out of 640 patients (0.31%) detected by PMS of CT-P13. Because tuberculosis developed in these 12 patients despite being examined (imaging, interferon-gamma release assay, or tuberculosis skin test) prior to IFX administration, continuous careful inspection should be required. The risk of tuberculosis associated with anti-TNF therapy has been extensively investigated, and the incidence was shown to be independent of disease type (CD or UC), age, and sex, but related to the local prevalence of latent tuberculosis and poverty.[9,12,16,34] The tuberculosis burden in Japan is intermediate, and 14 tuberculosis cases (0.28%) were reported in 5000 Japanese patients with rheumatoid arthritis in a large-scale PMS of the originator IFX.[35] Among them, 11 cases occurred in the first 2000 patients just after the introduction of IFX into the Japanese market, but the incidence was reduced to three per the remaining 3000 patients because of appropriate instruction regarding examinations and prophylactic drug use. Because the observation period was only 6 months, which is too short to detect all tuberculosis cases, the incidence of tuberculosis was estimated to be 0.20/100 person-years in the latter population. On the other hand, in our study, the observation period was 2 years, and the similar incidences of tuberculosis were estimated, that is, 0.16 and 0.12/100 patient-years for CT-P13 in PMS and the originator

Table 3 Incidence of tuberculosis and background of the patients who developed tuberculosis after the treatment with CT-P13 in PMS or the originator IFX in DBS

	CT-P13 in PMS	Originator IFX in DBS	*P* value
Occurrence of tuberculosis	(*n* = 640)	(*n* = 4113)	
Number of occurrences	2 (0.31%)	10 (0.24%)	0.75[‡]
Time to tuberculosis onset (days)	42, 303	154 (21–694)[†]	0.67[§]
HR (95% CI)	1.70 (0.37–7.82)	Reference	0.49[¶]
Characteristics of tuberculosis patients	(*n* = 2)	(*n* = 10)	
Male: female	2: 0	7: 3	
Age (years)	61, 61	34 (13–71)[†]	
CD: UC	1: 1	6: 4	
No prior biologics (naïve)	2 (100%)	6 (60%)	
Tuberculosis history	1 (50%)	4 (40%)	
Prophylactic use of isoniazid	0 (0%)	2 (20%)	
Prior chest radiograph or CT	2 (100%)	10 (100%)	
Prior examination of IGRA or TST	2 (100%)	7 (70%)	

[†]Values are expressed as median (range).
[‡]χ^2 test.
[§]Wilcoxson rank sum test.
[¶]Univariate Cox regression analysis.
HR, hazard ratio; CI, confidence interval; CT, computed tomography; DBS, database search; IFX, infliximab; IGRA, interferon-gamma release assay; PMS, post-marketing surveillance; TST, tuberculosis skin test.

Table 4 Incidence of drug-induced hepatic injury and resulting drug continuity of CT-P13 in PMS or the Originator IFX in DBS

	CT-P13 in PMS	Originator IFX in DBS	OR (95% CI)[†]	*P* value
Patients with increased ALT or ALP[‡]				
Total	104/563 (18.5%)	61/396 (15.4%)	1.24 (0.88–1.76)	0.22
No prior biologics (naïve)	52/228 (22.8%)	38/145 (26.2%)	0.83 (051–1.35)	0.45
Prior IFX (nonmedical switch)	33/241 (13.7%)	—	1.57 (0.89–2.77)	0.12
(continued treatment)	—	23/251 (9.2%)		
Treatment continuity after increase in ALT or ALP				
Continued	84/104 (80.8%)[§]	51/61 (83.6%)	1.21 (0.53–2.80)	0.65
Discontinued	20/104 (19.2%)[¶]	10/61 (16.4%)		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CI, confidence interval; DBS, database search; IFX, infliximab; OR, odds ratio; PMS, post-marketing surveillance.
[†]Odds ratio of CT-P13 in PMS to originator IFX in DBS (reference) by univariate logistic regression analysis.
[‡]Diagnostic criteria for drug-induced liver injury of Japan Society of Hepatology and the common standard values proposed by Japanese Committee for Clinical Laboratory Standards were applied.
[§]Recovery of ALT and ALP was confirmed in 79/104 (76.0%) patients.
[¶]Only one patient was discontinued because of liver damage. Hepatic disorder was reported in another three patients but was not considered the direct cause of discontinuation.

IFX in DBS, respectively. There might not be a difference in the economic background of these two cohorts, because the co-payments by IBD patients were the same for the biosimilar and originator due to the Intractable Disease Financial Assistance Program in Japan.

The incidence of liver injury caused by CT-P13 in PMS was comparable with that caused by the originator IFX in DBS (18.5% *vs* 15.4%). Furthermore, most of the patients with liver injury could continue treatment with CT-P13 or originator IFX (80.8% *vs* 83.6%). According to review articles on IFX-related hepatotoxicity, the incidence of liver damage was significant but relatively infrequent, spontaneous resolution was common, and prognosis was good after drug discontinuation.[10,36,37] Correspondingly, prescribing information for IFX in the United States and European Union includes cautions regarding elevation of hepatic markers and the possibility of treatment continuity, while there is no detailed description of the elevation of hepatic markers in the Japanese package insert for IFX. Our study indicated that the IFX-induced liver injury observed in Western patients has also occurred in Japanese patients and the administration of IFX could be continued in many cases, although careful observation is required. This similarity in occurrence of IFX-induced liver injury between patients overseas and patients in Japan, where the hepatitis virus infection rate is high, might be due to implementation of HBV/HCV screening and prophylactic treatment recommended by the Japanese guideline.[38]

In the two randomized controlled studies reported to date comparing CT-P13 with the originator IFX in IBD, the biosimilar

was shown to be noninferior to its originator.[3,4] However, in randomized controlled trials, the number of patients and the terms and conditions of patient registration are strictly specified, and thus, this situation does not reflect real-world practice. In contrast, while PMS and DBS provide robust information about the diverse general patient population, the amount of information on each patient is much less and sparse.[18,39] In our long-term PMS, information on 640 IBD patients could be collected, but the critical issue is lack of reference data on originator IFX to verify whether the biosimilar is equivalent to the originator. The single-arm study comparing clinical trial data to synthetic external control data from a database has been proposed as a novel alternative to randomized comparative study.[19] This approach could be biased and has other limitations compared with randomized controlled trials and therefore, should be limited to cases where setting an appropriate control group is difficult for ethical or feasibility reasons. Because our PMS has no control arm for practical reasons, we applied the above concept and utilized a Japanese administrative database to conduct a DBS for acquisition of a set of external reference data on originator IFX over the period covered by the PMS study.

This study has several limitations. First, comparison of data from different sources is naturally biased. Because there has been a paradigm shift in the clinical management of IBD over the past two decades, PMS data of the originator IFX conducted in Japan were too outdated to compare with our recent CT-P13 data. To minimize this bias and gaps in historical data, we stratified patients into subgroups according to the prior biologic therapy and IBD types (CD and UC) and matched the surveillance period. Second, searchable clinical items were limited in the database, which includes only the records of treatments and examinations provided, but not the results. We carefully established appropriate search algorithms to detect onset of tuberculosis. Finally, retrievable data from database were sparse. In fact, in our DBS, hepatic enzyme values were collected for only 9.6% of IBD patients. However, these data were not intentionally extracted, and it is likely that no selection bias was present.

From our comparison of long-term PMS data of CT-P13 with external reference data from an administrative database, we conclude that the biosimilar and the originator were similarly useful in real-world clinical practice and that the biosimilar had the same safety profile as the originator and could be used even in areas where tuberculosis and virus hepatitis occur frequently. In tuberculosis endemic area, even with negative tuberculosis screening results, attention should be paid to the occurrence of tuberculosis during the course of CT-P13 therapy as well as originator IFX.

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Data availability statement. The corresponding author (KN) and the coauthor (FY) had full access to all the data in the study. The study data are available on request from the authors.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Persistence of CT-P13 treatment and reasons for drug discontinuation in PMS.
Table S2. Incidence of ADRs leading to discontinuation of CT-P13 in 640 IBD patients in PMS during an observation period of 742.7 person-years.