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Safety and effectiveness of ustekinumab in Crohn's disease: Interim results of post-marketing surveillance in Japan

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Author contribution: TM and SY were involved in conception of the study. HT, TA, and SY were involved in study methodology. TM, HT, TA, and SY were involved in data analysis.

Abstract

Background and Aim: Ustekinumab, a human anti-interleukin-12/23 monoclonal antibody, has been approved in Japan for the treatment of Crohn's disease. Here, we report the findings from an 8-week interim analysis of post-marketing surveillance to evaluate the safety and effectiveness of ustekinumab in Japanese patients with Crohn's disease.

Methods: Patients initiating ustekinumab treatment were prospectively evaluated from May 2017 to June 2020 at 91 medical centers in Japan. Adverse drug reactions (ADRs) and serious ADRs (SADRs) were monitored. Effectiveness was evaluated by clinical response, clinical remission, and changes in Crohn's Disease Activity Index (CDAI) and C-reactive protein (CRP) from baseline to week 8. Presence of perianal disease was documented at baseline and week 8.

Results: In total, 341 patients were enrolled in the study, of which 339 were included in the safety analysis while 334 were included in the effectiveness analysis. The overall incidences of ADRs and SADRs were 5.3% and 2.1%, respectively. Worsening of Crohn's disease was the most common event. The clinical response and clinical remission rate at week 8 were 40.0% and 48.5%, respectively. Significant improvements in CDAI and serum CRP ($P < 0.001$) were observed at week 8. CDAI decreased significantly (mean difference: −31.4; 95% confidence interval: −61.1, −1.7; $P = 0.038$) in biologics-naïve patients *versus* patients who had received two or more biologics.

Conclusions: This 8-week interim analysis of the real-world study confirmed the effectiveness of ustekinumab-based therapy in Japanese patients with Crohn's disease. No new safety concerns were found during 8-week induction period in the Japanese clinical settings.

HT and SY were involved in visualization. SY was also involved in acquisition of funds and project administration. SY, TA, KN, HT, MT, ST, NM, and TM were involved in draft review and editing. All authors have approved the final manuscript for submission.

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by repeated cycles of relapsing and remitting granulomatous inflammations and fistulas, most typically occurring in the small intestine, the colon (especially the ileocecal region), and the perianal region.[1] The prevalence of CD has been believed to be much lower in Asian countries, including Japan, than in Western countries. However, recent epidemiological studies have suggested that CD incidence is rapidly increasing in Japan.[2,3] The estimated number of CD patients throughout Japan in 2014 was calculated to be 70 700 with an annual prevalence of 55.6 per 100 000 population.[2]

At present, no treatments can completely cure CD. The current treatment strategies emphasize to control the symptoms, prevent irreversible gastrointestinal damage and disability, attain sustained clinical remission, and thus improve quality of life.[4] Until the development of anti-tumor necrosis factor-α (anti-TNFα) agents, enteral nutritional therapy had been a primary therapy for CD in Japan.[5] The current pharmacotherapeutic options for CD in

Japan include corticosteroids as induction regimen and 5-aminosalicylic acid (5-ASA), immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP]), and biologics (TNFα antagonists, such as infliximab [IFX] and adalimumab [ADA]) for induction and maintenance.[6] Although anti-TNFα agents are highly effective for the induction and maintenance of remission in moderate-to-severe CD, several studies have reported primary or secondary loss of response and intolerance among patients with active CD.[7–10] In such cases, treatment optimization using dose escalation, shortening of the interval of administration, or switching of biologics needs to be considered. In addition, these maintenance biologics have been associated with serious adverse events (AEs) such as infections and malignancies.[11]

Ustekinumab (UST), a monoclonal antibody that binds to the p40 subunit of human interleukin-12/23, has been approved in Japan as a third biologic after IFX and ADA. The drug has been used for the treatment of moderate-to-severe active CD in patients who had an inadequate response to conventional therapies. Although the efficacy and safety of UST have been previously established in randomized controlled phase-2 (CERTIFI)[12] and phase-3 (UNITI-1, UNITI-2, and IM-UNITI) studies in patients with moderate-to-severe CD,[13,14] more knowledge on patient-reported outcomes is required to guide physicians in real-world settings. A few real-world data have been published recently from the Western countries[15–20]; however, limited data are available for Japanese patients receiving UST.[21,22]

This post-marketing surveillance (PMS) was designed to monitor the real-world safety and effectiveness of the long-term use (52 weeks) of UST in Japanese patients with CD. We conducted an 8-week interim analysis of the PMS data obtained from all patients who had received UST in routine clinical practice for the treatment of moderate-to-severe CD after its introduction in Japan. In addition, factors affecting the safety and effectiveness of UST were investigated.

Methods

Study design and participants. This survey was conducted based on a central registration method from May 2017 in accordance with Good Post-Marketing Study Practice. This interim analysis includes data up to 8 weeks from 91 different medical institutions in Japan with the cut-off date of June 30, 2020. The study protocol was reviewed by Institutional Review Board. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements.

Patients with CD, who initiated UST intravenous (IV) treatment and who had not been previously treated with UST, were eligible for inclusion in this study. Patients aged < 15 years were excluded from the effectiveness analysis. Patients received weight-based, one-time IV infusion induction dose of UST (260 mg [$\leq$ 55 kg] or 390 mg [$>$ 55 to 85 kg] or 520 mg [$>$ 85 kg]), followed by 90-mg subcutaneous (SC) maintenance injection every 8 or 12 weeks according to clinical judgment. The observation period was from the first dose of UST IV infusion to week 52 after the start of treatment. In case of completion (until patient showed improvement) or discontinuation of treatment (due to disease progression, onset of AE, withdrawal of consent, death, transfer to another hospital, or treatment withdrawal in case of $>$ 24 weeks of wash-out period), the observation period was until the date of treatment completion or discontinuation. Regardless of the continuation of treatment, patients were followed up for 3 years from the first dose of UST IV infusion to investigate the incidence of malignancy.

Data collection. Physicians registered each patient included in the survey via the registration forms of the Electronic Data Capture (EDC) system and sent the information within 14 days after the first dosing date of UST. Physicians entered the data into the EDC system for all registered patients from baseline before the first dosing to the end of the 52-week observation period or at discontinuation.

The survey items included the following demographic and baseline characteristics: gender, age, bodyweight, body height, time of onset and duration of CD, disease location and behavior, presence of perianal disease, history of UST use, history of any surgical procedures, history of smoking, history of prior and/or concomitant treatments, and presence/absence of active tuberculosis or serious infections. Baseline data for disease location (ileal/colonic/ileocolonic/other) and behavior (non-stricturing, non-penetrating/stricturing/penetrating) were collected and classified based on Japanese guidelines.[23] Although the presence of concomitant perianal disease is not included as a subcategory for the classification of disease behavior as per the Japanese guidelines (unlike Montreal classification system[24]), we have collected this information independent of the classification.

Safety endpoints and assessment. For the safety evaluation, AEs (defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality), serious AEs (SAEs), adverse drug reactions (ADRs, defined as AEs for which a causal relationship with the UST treatment could not be ruled out), and serious ADRs (SADRs) were recorded. All ADRs and SADRs including abnormal laboratory parameters related to ADRs that occurred during the survey period were recorded and coded according to system organ class (SOC) using Medical Dictionary for Regulatory Activities version 23.0.

Specifics about the ADRs including the type, date of onset, seriousness, treatment, outcome, and causal relationship with the administration of UST were investigated. Incidence of events of special interest, including serious hypersensitivity reactions, serious infections, tuberculosis, interstitial lung diseases, malignancy, and demyelinating inflammatory disease, was documented.

Effectiveness endpoints and assessments. Key effectiveness endpoints were clinical response (defined as reduction from baseline in the CD Activity Index [CDAI] score of $\geq$ 100 points) and clinical remission (defined as a CDAI score of $\leq$ 150) at week 8. Patients with a baseline CDAI score of $\geq$ 220 to $\leq$ 248 were considered to be in clinical response if a CDAI score of $<$ 150 was attained.[12] For the assessment of the clinical response and remission, patients with a CDAI $\leq$ 150 at baseline were excluded. Other endpoints included change from baseline to week

8 in CDAI score, C-reactive protein (CRP), and physician's global assessment (PGA) categorized as effective, partially effective, not effective, and undeterminable.

Factors associated with effectiveness at week 8 were investigated using the following subgroups: prior use of biologics (no/yes), concomitant use of steroids or immunomodulators (no/yes), location (ileal/colonic/ileocolonic/other), behavior (non-stricturing, non-penetrating/stricturing/penetrating), and perianal disease (no/yes).

Statistical analyses. The target number of patients in safety analysis was set as 300 in order to detect at least one case of an ADR with the incidence of 1% with a probability of 95% or higher. Data from all patients who received at least one dose of UST were used for the safety analysis. Patients with incomplete data or protocol violations were excluded from both safety and effectiveness analyses.

Two categories of factors were compared using Fisher's exact test while three or more categories were compared using the χ^2 test. For CDAI analysis, missing values were imputed using the last observation carried forward method. Changes in CRP and CDAI from baseline to week 8 were analyzed using the paired *t*-test. Group means were compared using independent *t*-test and estimation of 95% confidence intervals (CIs). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Japan Ltd.), without any imputation for missing data except for CDAI analysis. All tests were performed with a two-sided significance level of 5%; $P < 0.05$ was defined as statistically significant.

Results

Patient disposition and characteristics. A total of 341 CD patients were enrolled in this study. Two patients were excluded because data-cleaning activities were not finalized for

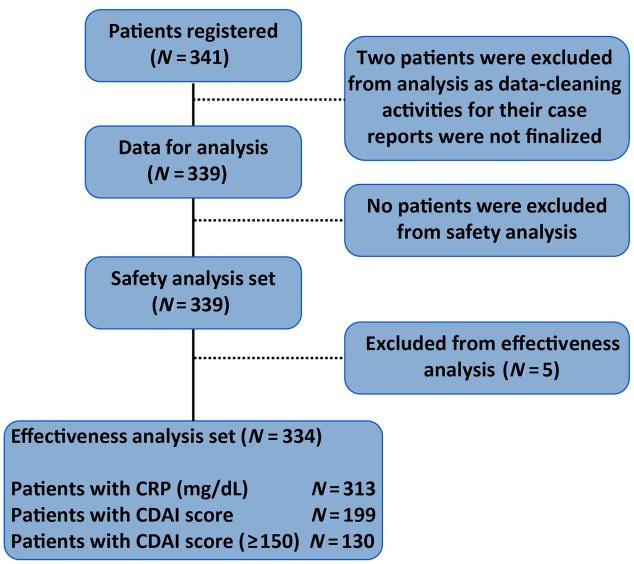

Figure 1 Patient disposition. CDAI, Crohn's Disease Activity Index; CRF, case report form; CRP, C-reactive protein.

Table 1 Patient demographics and baseline characteristics (safety analysis set)

Parameter	*N* = 339
Age, years	37.2 (13.4)
Gender, men	228 (67.3)
BMI, kg/m^2	20.7 (3.8)
Duration of disease, years	11.0 (9.1)
Smoking history	
No	237 (69.9)
Yes	63 (18.6)
Continue smoking	36 (57.1)
Disease location	
Ileocolonic	235 (69.3)
Ileal	67 (19.8)
Colonic	39 (11.5)
Others	1 (0.3)
Disease behavior	
Non-stricturing, non-penetrating	177 (52.2)
Stricturing	152 (44.8)
Penetrating	72 (21.2)
Perianal disease	66 (19.5)
Comorbidities	
No	238 (70.2)
Yes	101 (29.8)
History of CD-related surgery	
No	186 (54.9)
Yes	153 (45.1)
Prior use of biologics	
No	94 (27.7)
Yes	245 (72.3)
1	19 (7.8)
≥ 2	226 (92.2)
Type of biologics used	
Infliximab	188 (76.7)
Adalimumab	124 (50.6)
Vedolizumab	1 (0.4)
Others	1 (0.4)
Prior use of other treatment	
No	49 (14.5)
Yes	290 (85.6)
5-ASA	236 (81.4)
Steroid	111 (38.3)
AZA	72 (24.8)
6-MP	0
Enteral nutrition	30 (10.3)
Antibiotics	20 (6.9)
Others	73 (25.2)
Concomitant medication	
No	53 (15.6)
Yes	286 (84.4)
5-ASA	233 (68.7)
Steroid	
No	235 (69.3)
Yes	104 (30.7)
Oral	101 (29.8)
Intravenous	5 (1.5)
Immunomodulator (AZA or 6-MP)	
No	271 (79.9)

(Continues)

Table 1 (Continued)

Parameter	*N* = 339
Yes	68 (20.1)
Enteral nutrition	29 (8.6)
Antibiotics	12 (3.5)
Others	73 (21.5)

Values are presented as mean (SD) or *n* (%) unless otherwise specified. 5-ASA, 5-aminosalicylic acid; 6-MP, 6-meracptopurine; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; SD, standard deviation.

their case reports, and the remaining 339 patients were included in the safety analysis. Of these, patients aged < 15 years ($n = 5$) were excluded from the effectiveness analysis (Fig. 1). All patients in the effectiveness analysis ($n = 334$) had PGA at baseline, whereas baseline CRP (mg/dL) and baseline CDAI score were recorded for 313 and 199 ($n = 130$ with baseline CDAI ≥ 150) patients, respectively.

Table 1 summarizes the characteristics of the safety population. Majority of patients were men (67.3%), and the mean disease duration was 11.0 ± 9.1 years. Approximately 70% of the patients with CD were ileocolonic type, and about half of the patients had non-stricturing/non-penetrating disease type (52.2%). Sixty-six patients (19.5%) had complication of perianal disease. Approximately 72% patients had previously received biologics that included IFX (76.7%), ADA (50.6%), or vedolizumab (VDZ) (0.4%). The reason for discontinuation of biologics in this study included primary nonresponse (around 15%), secondary loss of response (around 60%), and AEs (around 23%). Concomitant medications were steroids (30.7%) and immunomodulators (20.1%) such as AZA and 6-MP.

Table 2 Incidence of adverse drug reactions

N = 339	ADR	SADR	Non-SADR
Number of patients	18	7	11
Number of events	24	7	17
Incident rate (%)	5.3	2.1	3.2
Common ADRs observed in > 0.5% patients, *n* (%)			
Worsening of CD	3 (0.9)	3 (0.9)	—
Pyrexia	2 (0.6)	—	2 (0.6)
Malaise	2 (0.6)	—	2 (0.6)
Upper respiratory tract inflammation	2 (0.6)	—	2 (0.6)

ADR, adverse drug reaction; CD, Crohn's disease; SADR, serious adverse drug reaction.

Safety. At week 8, the overall incidence of ADRs and SADRs in the safety population was 5.3% and 2.1%, respectively. The incidence of ADRs by SOC was highest for worsening of CD (0.9%), followed by pyrexia, malaise, and upper respiratory tract inflammation (each 0.6%). The most frequently reported SADR was worsening of CD (0.9%, $n = 3$) (Table 2). Of the three patients, two discontinued UST treatment at week 8 and the other patient continued to receive UST after week 8 (Table S1). No significant difference was observed in the incidence of ADRs between patients stratified by prior use of biologics, concomitant use of steroids, or immunomodulators (AZA or 6-MP) (Fig. 2). Two serious infection events were observed: anal abscess and pneumonia ($n = 1$ each); both were AEs of special interest and categorized as SADRs. No other events of special interest were reported.

Effectiveness. The rates of clinical response (decrease in CDAI ≥ 100 points) and clinical remission (CDAI ≤ 150) at week 8 were 40.0% and 48.5%, respectively (Fig. 3a). Both CDAI and CRP decreased significantly ($P < 0.001$) at week 8 (Fig. 3b,c). Figure S1 shows distribution of the patients with CDAI both at baseline and at week 8.

Prior use of anti-TNF agents (*vs* no use) was associated with significant reduction (mean difference: −31.3; 95% CI: −60.0, −2.6; $P = 0.033$) in CDAI score (Fig. 4). CDAI score decreased significantly (mean difference: −31.4; 95% CI: −61.1, −1.7; $P = 0.038$) in anti-TNF-naïve patients *versus* patients who had received two

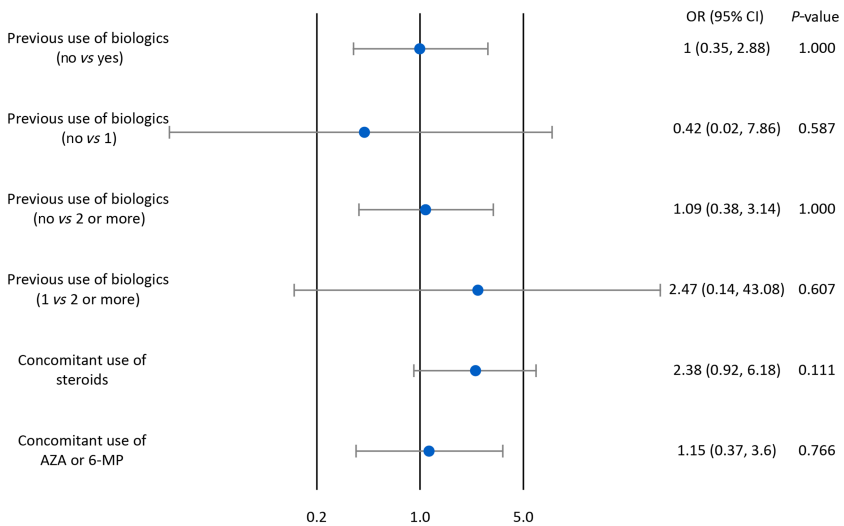

Figure 2 Factors affecting the safety of ustekinumab identified by odds ratio for adverse drug reactions. Confidence interval was calculated by exact method. *P*-value was calculated using Fisher's exact test. 6-MP, 6-mercaptopurine; AZA, azathioprine; CI, confidence interval, OR, odds ratio.

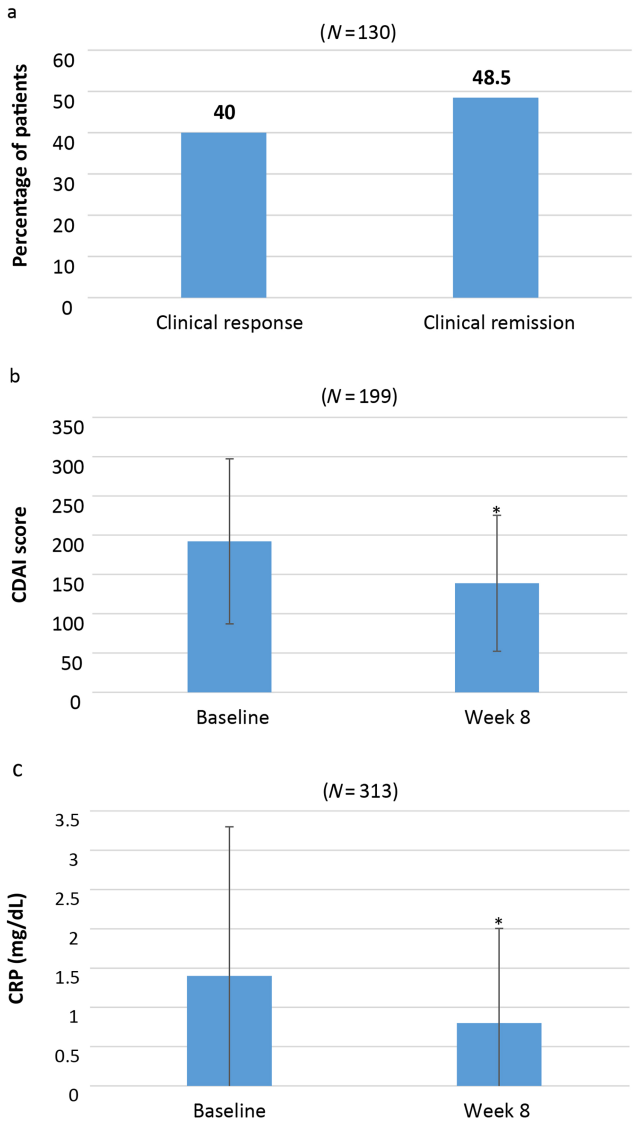

Figure 3 Effectiveness of ustekinumab from baseline to week 8: (a) Rate of clinical response and clinical remission. (b) Change in CDAI score. (c) Change in CRP level. *$P < 0.001$. For the assessment of the clinical response and remission, patients with CDAI ≤ 150 at baseline were excluded. *P*-value was calculated using paired *t*-test. CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein.

or more TNF antagonists (Fig. 4). No significant differences were observed in the effectiveness of UST in the subgroups of patients with or without concomitant use of steroids or immunomodulators (Fig. 4). Reduction in CDAI score was not different when patients were classified by disease location or behavior (Fig. 5). Perianal disease was reported in 65 patients at the baseline, of whom 47 patients showed presence of disease at 8 weeks (Fig. S2).

General improvement rate was scored by the PGA using the categories being effective, partially effective, not effective, and undeterminable. All patients in the effectiveness analysis (n = 334) had PGA assessments at baseline. UST-based therapy was found to be effective in 135/334 (40.4%), partially effective in 157/334 (47.0%), not effective in 31/334 (9.3%), and undeterminable in 11/334 (3.3%) patients (Fig. S3).

Discussion

This 8-week interim analysis of the PMS demonstrated the safety and effectiveness of UST in real-world clinical practice for the treatment of CD in Japan.

In the present study, the frequency of ADRs and SADRs was generally low following 8 weeks of UST induction. The safety of UST was established in a Japanese subpopulation analysis of phase-3 UNITI studies; nasopharyngitis and pyrexia were the most common AEs during UST induction, with no reports of serious infections.[14] A real-world study in Japan reported the frequency of AEs up to 9.5%, with abdominal pain and general fatigue being the most common AEs.[22] In other real-world studies, the most common AEs reported were skin disorders, systemic infections, joint pain, and local abscesses.[15–17,19,20,25–29] The safety profile of UST has been well established in patients with psoriasis (PSOLAR registry), with reassuring long-term data.[30] The safety findings in the present study were consistent with the known safety profile of UST in induction phase, and no new safety signals were identified. With the use of UST becoming more common in the treatment of IBD, these findings will be beneficial to practitioners to assess the risks *versus* benefits of UST. Nevertheless, because this interim analysis only includes safety data for the 8-week induction period, a final analysis of this study with 52-week data is warranted to evaluate long-term safety of UST in the treatment of patients with CD.

In this study, effectiveness of UST in Japanese patients was demonstrated by significant reduction in CDAI score at 8 weeks following UST induction. The rates of clinical response and clinical remission at 8 weeks were 40.0% and 48.5%, respectively. The efficacy of UST in CD has been previously established in the phase-3 UNITI trials.[12,13,31] Several real-world observational studies have assessed clinical response and remission following UST induction therapy.[17,21,22,27,28] Overall, our results are in line with previously published real-world studies. However, our study had several differences in patients' background and the assessment of effectiveness. Among patients with baseline CDAI score, about 35% of the patients had CDAI < 150 at baseline and were included in this study. Therefore, to investigate the effectiveness of UST on active CD, patients with CDAI ≥ 150 and CDAI ≥ 220 at baseline were subjected to assessment of clinical remission and response, respectively. Also, patients achieving clinical response did not include those with CDAI score reduction from 150 ≤ CDAI < 220 at baseline to CDAI < 150 at week 8. This might be associated with lower rate of clinical response than that of clinical remission. Furthermore, approximately more than 70% of anti-TNF-exposed patients and one patient with prior VDZ exposure were included in our study. Almost all of them were exposed to two or more biologics. The study population in our study differed from those in the other reports in terms of proportion of VDZ-exposed population. This might be due to the fact that UST has been approved and introduced first in the Japanese market followed by VDZ. While differences in the population between the UNITI trials[13] and other real-world reports

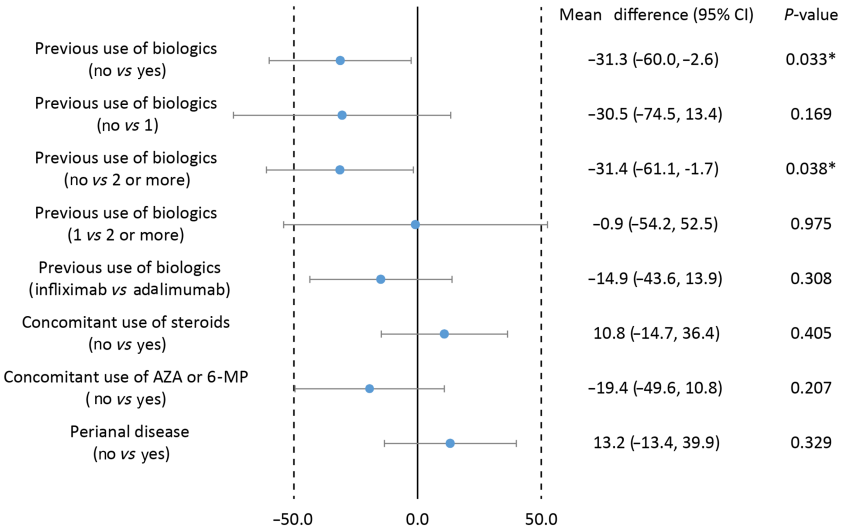

Figure 4 Factors affecting the effectiveness of ustekinumab identified by mean difference of change of CDAI score from baseline to week 8. $*P < 0.05$ was defined as statistically significant. Confidence interval was calculated by normal distribution. *P*-value was calculated using independent *t*-test. 6-MP, 6-mercaptopurine; AZA, azathiophine; CDAI, Crohn's Disease Activity Index; CI, confidence interval.

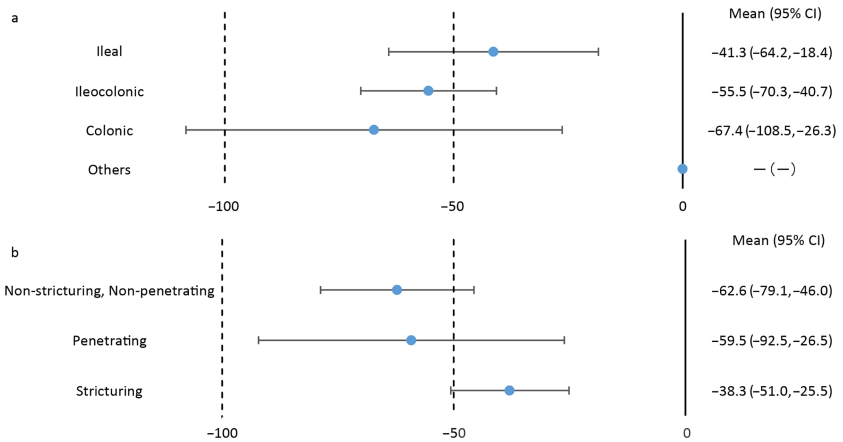

Figure 5 Effect of (a) disease location and (b) disease behavior on effectiveness of ustekinumab identified by mean change of CDAI score from baseline to week 8. Confidence interval was calculated by normal distribution. CDAI, Crohn's Disease Activity Index; CI, confidence interval.

(i.e. biologics and VDZ failure population)[15,17] may have contributed to a difference in clinical outcomes, our findings were similar to the previous observations.

Interleukin-23 represents a suitable molecular target in anti-TNF refractory CD[32]; thus, prior failure to anti-TNF therapy could be associated with better clinical response to UST.[33] Furthermore, UST showed better effectiveness when compared with VDZ in CD patients with prior failure to anti-TNF treatment.[34–36] Most of the published evidence has focused on anti-TNF-experienced population. The present study included about 30% of biologic-naïve population and almost 70% of biologic-experienced population, the majority of whom had prior exposure to more than two biologics. Subgroup analysis demonstrated a significant decrease in CDAI score from baseline in biologic-naïve patients compared with those who had prior exposure to two or more biologics, suggesting the benefit of UST as the first-line biologic for CD treatment. A recent report has suggested that UST as the first-line biologic therapy yields to greater quality of life than later use in the CD course.[37] However, the efficacy of UST as first-line biologic has not been fully examined in naïve patients, and there could be various factors, including disease severity, presence of extraintestinal manifestations, concomitant drugs, cost-effectiveness, and dosing schedule affecting the efficacy. These predictors of the treatment efficacy may aid the clinical decision-making for appropriate positioning of UST in treatment algorithms for CD.

Perianal disease is a common and clinically significant complication of CD. Compared with Western countries, presence of perianal disease at the time of diagnosis is encountered more frequently in Asian countries.[38] In contrast, in this study, only about 20% of the CD patients showed presence of perianal disease when UST therapy was initiated. This observation might be related to lower CDAI score at baseline in our study compared with other reports or limited population of UST therapy. A post-hoc analysis demonstrated efficacy in fistula healing across the three pivotal UST induction studies in patients with active perianal fistulas.[39] Few real-world studies have also evaluated the effectiveness of UST in perianal CD.[26,29,40] The BioLAP Study Group demonstrated effectiveness of UST in perianal CD whereas VDZ showed low rates of response in patients with active perianal CD.[41,42] In the present study, number of the CD patients with perianal disease was decreased 8 weeks after UST administration in Japanese population, suggesting the possibility of beneficial effects of UST on perianal disease. However, as the perianal disease was not assessed by either physical or radiological examination in this study, further investigation is warranted.

There are some limitations in our study. First, because the present analyses were based on data collected at 8 weeks after administration of UST, there were very few cases in which endoscopy was performed, and therefore, the assessment of mucosal healing could not be included in this analysis. However, results of 52 weeks after the administration of UST, which are currently being collected, will provide further information. Second, although we showed a reduction in the number of patients with perianal disease at 8 weeks after UST administration, we were unable to investigate the effectiveness of UST on perianal manifestations in detail because the nature of PMS does not allow for a placebo group. Future prospective studies or at least analysis of larger real-world data that rigorously match the patient background are needed.

In conclusion, this study demonstrated effectiveness and safety of UST in the induction phase for treatment of CD in real-world clinical practice in Japan. UST was well tolerated in this study; however, long-term results are warranted to fully investigate the safety profile and effectiveness of UST in real-world settings. Currently, the study for the maintenance period is ongoing, and long-term data will be available in the future.

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References

1 Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741–55.
2 Murakami Y, Nishiwaki Y, Oba MS *et al*. Estimated prevalence of ulcerative colitis and Crohn's disease in Japan in 2014: an analysis of a nationwide survey. *J. Gastroenterol.* 2019; **54**: 1070–7.
3 Ng WK, Wong SH, Ng SC. Changing epidemiological trends of inflammatory bowel disease in Asia. *Intest. Res.* 2016; **14**: 111–9.
4 Cheifetz AS. Management of active Crohn disease. *JAMA* 2013; **309**: 2150–8.
5 Hiwatashi N. Enteral nutrition for Crohn's disease in Japan. *Dis. Colon Rectum* 1997; **40**: S48–53.
6 Ueno F, Matsui T, Matsumoto T, Matsuoka K, Watanabe M, Hibi T. Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *J. Gastroenterol.* 2013; **48**: 31–72.
7 Colombel JF, Sandborn WJ, Rutgeerts P *et al*. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52–65.
8 Hanauer SB, Feagan BG, Lichtenstein GR *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541–9.
9 Hanauer SB, Sandborn WJ, Rutgeerts P *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I Trial. *Gastroenterology* 2006; **130**: 323–33.
10 Sandborn WJ, Feagan BG, Stoinov S *et al*. Certolizumab pegol for the treatment of Crohn's disease. *N. Engl. J. Med.* 2007; **357**: 228–38.
11 Papamichael K, Mantzaris GJ, Peyrin-Biroulet L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease. *Expert Opin. Drug Saf.* 2016; **15**: 493–501.
12 Sandborn WJ, Gasink C, Gao L-L *et al*. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N. Engl. J. Med.* 2012; **367**: 1519–28.
13 Feagan BG, Sandborn WJ, Gasink C *et al*. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* 2016; **375**: 1946–60.
14 Hibi T, Imai Y, Murata Y, Matsushima N, Zheng R, Gasink C. Efficacy and safety of ustekinumab in Japanese patients with moderately to severely active Crohn's disease: a subpopulation analysis of phase 3 induction and maintenance studies. *Intest. Res.* 2017; **15**: 475–86.
15 Biemans VB, van der Meulen-de Jong AE, Van Der Woude CJ *et al*. Ustekinumab for Crohn's disease: results of the ICC registry, a nationwide prospective observational cohort study. *J. Crohns Colitis* 2020; **14**: 33–45.
16 Bar-Gil Shitrit A, Ben-Ya'acov A, Siterman M *et al*. Safety and effectiveness of ustekinumab for induction of remission in patients with Crohn's disease: a multicenter Israeli study. *United Eur. Gastroenterol. J.* 2020; **8**: 418–24.
17 Iborra M, Beltrán B, Fernández-Clotet A *et al*. Real-world short-term effectiveness of ustekinumab in 305 patients with Crohn's disease: results from the ENEIDA registry. *Aliment. Pharmacol. Ther.* 2019; **50**: 278–88.
18 Engel T, Yung DE, Ma C *et al*. Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence. *Dig. Liver Dis.* 2019; **51**: 1232–40.
19 Eberl A, Hallinen T, Af Björkesten C-G *et al*. Ustekinumab for Crohn's disease: a nationwide real-life cohort study from Finland (FINUSTE). *Scand. J. Gastroenterol.* 2019; **54**: 718–25.
20 Wils P, Bouhnik Y, Michetti P *et al*. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Aliment. Pharmacol. Ther.* 2018; **47**: 588–95.
21 Miyazaki T, Watanabe K, Kojima K *et al*. Efficacies and related issues of ustekinumab in Japanese patients with Crohn's disease: a preliminary study. *Digestion* 2020; **101**: 53–9.
22 Ito T, Maemoto A, Katsurada T *et al*. Long-term clinical effectiveness of ustekinumab in patients with Crohn's disease: a retrospective cohort study. *Crohn's & Colitis 360* 2020. https://doi.org/10.1093/crocol/otaa061
23 Matsuoka K, Kobayashi T, Ueno F *et al*. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J. Gastroenterol.* 2018; **53**: 305–53.
24 Satsangi J, Silverberg M, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749–53.
25 Harris RJ, McDonnell M, Young D *et al*. Early real-world effectiveness of ustekinumab for Crohn's disease. *Frontline Gastroenterol.* 2020; **11**: 111–6.
26 Khorrami S, Ginard D, Marín-Jiménez I *et al*. Ustekinumab for the treatment of refractory Crohn's disease: the Spanish experience in a large multicentre open-label cohort. *Inflamm. Bowel Dis.* 2016; **22**: 1662–9.
27 Kubesch A, Rueter L, Farrag K *et al*. Short and long-term effectiveness of ustekinumab in patients with Crohn's disease: real-world data from a German IBD cohort. *J. Clin. Med.* 2019; **8**: 2140.
28 Liefferinckx C, Verstockt B, Gils A *et al*. Long-term clinical effectiveness of ustekinumab in patients with Crohn's disease who

failed biologic therapies: a national cohort study. *J. Crohns Colitis* 2019; **13**: 1401–9.
29 Ma C, Fedorak R, Kaplan G *et al*. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. *Aliment. Pharmacol. Ther.* 2017; **45**: 1232–43.
30 Papp K, Gottlieb AB, Naldi L *et al*. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J. Drugs Dermatol.* 2015; **14**: 706–14.
31 Sandborn WJ, Rutgeerts P, Gasink C *et al*. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment. Pharmacol. Ther.* 2018; **48**: 65–77.
32 Schmitt H, Billmeier U, Dieterich W *et al*. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. *Gut* 2019; **68**: 814–28.
33 Greenup A-J, Rosenfeld G, Bressler B. Ustekinumab use in Crohn's disease: a Canadian tertiary care centre experience. *Scand. J. Gastroenterol.* 2017; **52**: 1354–9.
34 Alric H, Amiot A, Kirchgesner J *et al*. The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor. *Aliment. Pharmacol. Ther.* 2020; **51**: 948–57.
35 Biemans VB, van der Woude CJ, Dijkstra G *et al*. Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment. *Aliment. Pharmacol. Ther.* 2020. https://doi.org/10.1111/apt.15745
36 Kassouri L, Amiot A, Kirchgesner J *et al*. The outcome of Crohn's disease patients refractory to anti-TNF and either vedolizumab or ustekinumab. *Dig. Liver Dis.* 2020; **52**: 1148–55.
37 Scott FI, Hans AK, Gerich ME *et al*. Identification of the most effective position for ustekinumab in treatment algorithms for Crohn's disease. *Clin. Gastroenterol. Hepatol.* 2020. https://doi.org/10.1016/j.cgh.2020.08.021
38 Park SJ, Kim WH, Cheon JH. Clinical characteristics and treatment of inflammatory bowel disease: a comparison of Eastern and Western perspectives. *World J. Gastroenterol.* 2014; **20**: 11525–37.
39 Sands BE, Gasink C, Jacobstein D *et al*. Fistula healing in pivotal studies of ustekinumab in Crohn's disease [Abstract]. *Gastroenterology* 2017; **152**: S185.
40 Wils P, Bouhnik Y, Michetti P *et al*. Subcutaneous ustekinumab provides clinical benefit for two-thirds of patients with Crohn's disease refractory to anti-tumor necrosis factor agents. *Clin. Gastroenterol. Hepatol.* 2016; **14**: 242–50.
41 Biron C, Seksik P, Nachury M *et al*. DOP74 Efficacy of ustekinumab in perianal Crohn's disease: the BioLAP multi-centre observational study [Abstract]. *J. Crohns Colitis* 2019; **13**: S074–5.
42 Chapuis-Biron C, Bourrier A, Nachury M *et al*. Vedolizumab for perianal Crohn's disease: a multicentre cohort study in 151 patients. *Aliment. Pharmacol. Ther.* 2020; **51**: 719–27.

Supporting information

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

Figure S1. Distribution of patients with CDAI at baseline and week 8, CDAI, Crohn's Disease Activity Index.

Figure S2. Change in the number of patients with perianal disease from baseline to week 8.

Figure S3. Physician's global assessment.

Table S1. Subsequent outcomes of three cases reported as SADR of worsening of CD.