Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.15992

ORIGINAL ARTICLE - GASTROENTEROLOGY (CLINICAL)

Long-term effectiveness of ustekinumab comparable to antitumor necrosis factor agents in patients with Crohn's disease

Hisashi Shiga,* Kunio Tarasawa,† Rintaro Moroi,* Motoki Makuuchi,* Takahiro Takahashi,* Yusuke Shimoyama,* Masatake Kuroha,* Yoichi Kakuta,* Kiyohide Fushimi,‡ Kenji Fujimori,† Yoshitaka Kinouchi§ and Atsushi Masamune*

*Division of Gastroenterology, †Department of Health Administration and Policy, Tohoku University Graduate School of Medicine, §Student Health Care Center, Institute for Excellence in Higher Education, Tohoku University, Sendai, ‡Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Bunkyo, Japan

Key words
adalimumab, anti-tumor necrosis factor, Crohn's disease, infliximab, ustekinumab.

Accepted for publication 30 August 2022.

Correspondence
Hisashi Shiga, MD, PhD, Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
Email: shiga@med.tohoku.ac.jp

Conflict of interest: HS received lecture fees from Mitsubishi Tanabe Pharma Corp., AbbVie Inc., EA Pharma Co. Ltd., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co. Ltd., and Pfizer Inc. YKa received research grants from AbbVie Inc., Daiichi Sankyo Co. Ltd., Kyowa Kirin Co. Ltd., PRECISION IBD, and Janssen Pharmaceutical K.K. and received lecture fees from Mitsubishi Tanabe Pharma Corp., and Janssen Pharmaceutical K.K. AM received research grants from Zeria Pharmaceutical Co. Ltd., JIMRO Co. Ltd., Mochida Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corp., AbbVie Inc., EA Pharma Co. Ltd., and Takeda Pharmaceutical Co. Ltd. and received lecture fees from AbbVie Inc., EA Pharma Co. Ltd. and Takeda Pharmaceutical Co. Ltd.

Abstract

Background: Ustekinumab (UST), an antibody against the p40 subunit of interleukin-12/23, has been proven to be effective in patients with Crohn's disease (CD). However, large, long-term comparative studies of UST against anti--tumor necrosis factor (TNF) agents are lacking. We compared the effectiveness of anti-TNF agents and UST in CD patients without prior use of biologics.

Methods: We used a large nationwide anonymized Japanese database containing administrative medical claims data and various related patient data. In a propensity score-matched cohort with similar clinical characteristics, 2-year effectiveness was compared between patients treated with infliximab or adalimumab (anti-TNF group) and those treated with UST (UST group). Primary outcomes were cumulative rates of hospitalization, surgery, and persistence.

Results: Among 53 540 CD patients, 7047 were extracted for eligibility, of which 5665 were treated with an anti-TNF agent and 1382 with UST. After propensity score matching, the cumulative hospitalization rates were comparable between anti-TNF and UST groups ($P = 0.85$; 25.3% *vs* 26.5% at 1 year, 33.8% *vs* 39.8% at 2 years). The cumulative surgery rates were also comparable between these groups ($P = 0.46$; 5.5% *vs* 5.1% at 1 year, 8.3% *vs* 8.4% at 2 years). The persistence rate at 1 year was higher in UST group (90.8% *vs* 92.5%), and that at 2 years was higher in anti-TNF group (81.2% and 74.6%); however, there was no significant difference in the cumulative persistence rate ($P = 0.55$).

Conclusions: Anti-TNF agents and UST appear to have comparable effectiveness for CD patients without prior use of biologics.

Author contributions: HS conceived the study, wrote the study protocol, collected and analyzed the data, and wrote the manuscript. KT, KFus, and KFuj collected and analyzed the data. MM, TT, YS, RM, MK, YKa, YKi, and AM contributed to discussions. All authors had full access to all the data in this study and approved the final version of the manuscript.

Introduction

Ustekinumab (UST) is an antibody against the p40 subunit of interleukin-12/23, and the efficacy and safety of UST in patients with Crohn's disease (CD) have been elucidated. The induction (UNITI-I and UNITI-II) and subsequent maintenance (IM-UNITI) studies demonstrated the efficacy of UST in patients with and without a history of failure following antitumor necrosis factor (TNF) agent therapy.[1] Long-term extension study up to 5 years following the IM-UNITI also demonstrated a high persistence rate for UST.[2] In these studies, the control group consisted of patients who received a placebo. Real-world data, especially from multicenter registry studies, have also shown the effectiveness of UST in patients with CD.[3–8] Because UST became available more than 10 years after anti-TNF agents, most of the reports on the effectiveness of UST targeted patients with a history of anti-TNF agent failure, and no control group was included. Network meta-analyses have indirectly compared the effectiveness of anti-TNF agents and UST in biologic-naïve and biologic-experienced patients[9,10]; however, there have been no

large-scale studies directly comparing the two agents because of their high costs.

Most recently, the first clinical trial directly comparing the efficacy of an anti-TNF agent (adalimumab [ADA]) and UST in biologic-naïve patients has been reported.[11–13] In this trial, the clinical remission rates at 52 weeks for the two agents were comparable. Despite not being the primary endpoint, the percentage of patients who discontinued treatment by week 52 because of a lack of efficacy or other reasons was lower in the UST group (15.2%) than in the ADA group (23.6%). The long-term course of this trial is promising; however, larger and longer-term comparative studies are warranted. The present study compared the effectiveness of anti-TNF agents and UST in patients with CD using a large nationwide database in Japan.

Materials and Methods

Diagnosis Procedure Combination system. In this study, we conducted a population-based retrospective cohort study using the Diagnosis Procedure Combination (DPC) system. DPC is a large nationwide anonymized database for inpatient care of acute care hospitals in Japan that was introduced in 2003, covering about 90% of acute care beds as of 2020 and now also providing information on outpatient care. This system contains Japanese administrative medical claims data and various related patient data, such as gender, age, diagnoses coded according to International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), comorbidities on admission, complications during hospitalization, drugs administered, and surgery or other procedure records. The DPC database contains inpatient data for approximately 8 million patients per year from more than 1200 hospitals and can also be connected to the outpatient care data of the same patient. This database has been maintained through funding from the Ministry of Health, Labour and Welfare of Japan and has already been validated for diagnoses and procedure records.[14] If patients are transferred to other hospitals or clinics, their claim data can no longer be collected and will be censored. We previously reported a study using the DPC database for a different colonic disease.[15] Using other administrative claims databases in Japan, similar studies of patients with ulcerative colitis on the use of steroids or immunomodulators have also been reported.[16,17]

The Ethics Committee of Tohoku University Hospital approved the study protocol on 13 January 2021 (No. 2021-1-029). There was no need to obtain informed consent because the data are anonymized.

Selection of eligible cases. We included patients with a diagnosis of CD using the ICD-10 codes K500, K501, K508, and K509 who received inpatient or outpatient care at hospitals with the DPC system from April 2018 to March 2020. Among patients with CD as their primary disease, we excluded those with confirmed diagnoses of concomitant diseases that could lead to the use of biologics (e.g., ulcerative colitis, rheumatoid arthritis) and those with a history of any biologic use within 6 months prior to the first administration of biologics to be evaluated.

The following information was collected as the patient's clinical characteristics: sex, age, date of CD diagnosis at the respective hospitals, date of the first administration of biologics (index date), surgery within 6 months prior to the index date, hospital type (academic hospitals or others), outpatient or inpatient status on the index date, type of biologics used, and concomitant medications (steroids and immunomodulators). Infliximab (IFX), ADA, and UST were included as biologics, whereas vedolizumab (VDZ) was excluded from the analysis because the number of patients treated with VDZ was extremely small because of the short period since its approval in Japan. In cases with loss of response requiring optimization of biologics (dose increase from 5 to 10 mg/kg or interval shortening from every 8 weeks to every 4 weeks for IFX, dose increase from 40 to 80 mg for ADA, and interval shortening from every 12 weeks to every 8 weeks for UST), the dose of each biologic agent and the time from index date to optimization were also collected. Immunomodulators were composed of azathioprine and 6-mercaptopurine.

Primary and secondary outcomes. We performed a propensity score (PS) matching method to eliminate the difference in clinical characteristics between the two groups: patients treated with IFX ADA (the anti-TNF group) and those treated with UST (the UST group). The primary outcomes were the times from biologics initiation to hospitalization (cumulative hospitalization rate), surgery (cumulative surgery rate), and treatment discontinuation (cumulative persistence rate). Short-term hospitalizations less than 3 days were excluded from the hospitalization outcome because hospitalizations for exacerbation of CD rarely take less than 3 days in Japan. Hospitalizations not related to CD relapse were also excluded from the hospitalization outcome. Non-CD-related surgeries or surgeries for perianal lesions alone were excluded from the surgery outcome. Discontinuation was defined as the cessation of continuous administration of the first biologic or a switch from the first biologic to a second one.

The primary outcomes (cumulative hospitalization, surgery, and persistence rates) analyzed separately for patients with and without immunomodulators were defined as secondary outcomes. In addition, after dividing the anti-TNF group into patients treated with IFX and those with ADA, primary outcomes were compared between the three groups (the IFX, ADA, and UST groups), which were also defined as secondary outcomes.

Statistical analysis. Data are presented as the mean and standard deviation (SD). Using the *t*-test, chi-squared test, or Fisher's exact probability test as appropriate, we assessed differences between the groups.

Based on the estimated PS of each patient, a PS matching method was used to compare the anti-TNF and UST groups. PS was estimated by multivariate logistic regression using covariates that may be involved in the choice of therapeutic agents at the start of biologic therapy. Covariates included sex, age, disease duration from the confirmed CD diagnosis to the index date, surgery within 6 months prior to the index date, hospital type (academic hospitals or others), outpatient or inpatient status on the index date, and concomitant medications (steroids and immunomodulators). Then, pairs of patients with similar backgrounds were selected by PS matching using the 1:1 nearest neighbor method with calipers. The caliper was set 0.2 times the standard deviation of the PS logit. Based on the c-statistics, the performance of PS estimation was

evaluated. The standardized difference was used to compare the covariates of the two groups after PS matching, and covariates between the two groups were considered to be well balanced if the standardized difference was <0.1. We compared the cumulative incidence of the primary outcomes (the cumulative hospitalization, surgery, and persistence rates as described previously) in the PS-matched cohorts.

These analyses were performed using the JMP Pro Ver. software program (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ indicated a statistically significant difference.

Results

Patient enrollment. From the 53 540 patients with a diagnosis of CD, we excluded 10 283 patients with comorbidities that might warrant the use of biologics consisting of 6104, 2032, 1154, 698, 229, 37, 15, and 14 patients with ulcerative colitis, rheumatoid arthritis, Behçet's disease, psoriasis, uveitis, ankylosing spondylitis, juvenile idiopathic arthritis, and Kawasaki disease, respectively. We also excluded 22 266 patients without a history of biologic use during the observation period and 13 772 patients with a history of biologic use within 6 months prior to the index date. As a result, 7219 patients who newly started biologic therapy during the observation period were extracted. After further excluding 172 patients treated with VDZ, 7047 patients were eligible for this analysis (Fig. 1). Of these patients, 5665 were treated with anti-TNF agents (2923 with IFX and 2742 with ADA), and the remaining 1382 were treated with UST.

Patients' clinical characteristics and medical treatments. The clinical characteristics of the 7047 patients included in this study are presented in Table 1. These patients included 5047

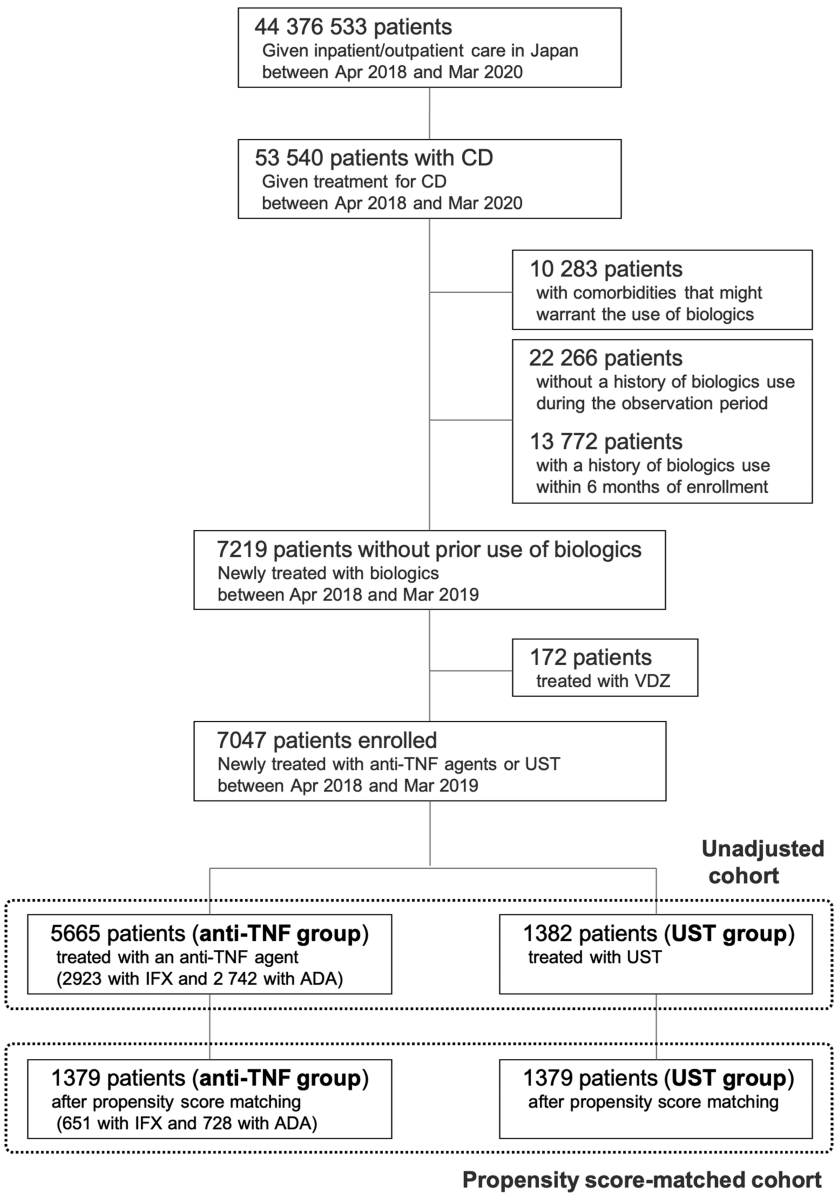


Figure 1 Patient flow in this study. From the 53 540 patients with confirmed diagnoses of Crohn's disease (CD), we excluded patients with comorbidities that might warrant the use of biologics, patients history of biologic use during the observation period, and patients with a history of any type of biologic use within 6 months prior to the study entry. After further excluding 172 patients treated with vedolizumab, 7047 patients were eligible for this analysis.

Table 1 Clinicopathological characteristics of patients treated with anti-TNF agents and UST in the unadjusted cohort and in the PS-matched cohort

Clinical characteristics†	Unadjusted cohort (*N* = 7047)			PS-matched cohort (*N* = 2758)			
	Anti-TNF (*N* = 5665)	UST (*N* = 1382)	*P* value	Anti-TNF (*N* = 1379)	UST (*N* = 1379)	*P* value	Standardized difference‡
Sex, *n* (%)							
Male	4093 (72.3%)	954 (69.0%)	0.018	959 (69.5%)	953 (69.1%)	0.836	0.009
Female	1572 (27.7%)	428 (31.0%)		420 (30.5%)	426 (30.9%)		
Age at enrollment							
(mean; years)	35.1	37.6	<0.001	37.4	37.6		0.013
(SD; years)	14.4	15.1		14.9	15.1		
Duration from CD diagnosis							
(mean; years)	3.3	3.4	0.621	3.3	3.4		0.017
(SD; years)	5.6	5.9		6.0	5.9		
Within 1 year from CD diagnosis, *n* (%)							
Yes	3041 (54.0%)	755 (54.7%)	0.608	798 (57.9%)	755 (54.7%)	0.107	0.065
No	2595 (46.0%)	624 (45.3%)		581 (42.1%)	624 (45.3%)		
Previous surgery within 6 months, *n* (%)							
Without	5331 (94.1%)	1208 (87.4%)	<0.001	1215 (88.1%)	1205 (87.4%)	0.601	0.021
With	334 (5.9%)	174 (12.6%)		164 (11.9%)	174 (12.6%)		
Hospital type, *n* (%)							
Academic hospitals	2016 (35.6%)	604 (43.7%)	<0.001	619 (44.9%)	603 (43.7%)	0.570	0.024
Others	3649 (64.4%)	778 (56.3%)		760 (55.1%)	776 (56.3%)		
Inpatient *vs* outpatient, *n* (%)							
Inpatient	1663 (29.4%)	427 (30.9%)	0.260	402 (29.2%)	424 (30.7%)	0.380	0.033
Outpatient	4002 (70.6%)	955 (69.1%)		977 (70.8%)	955 (69.3%)		
Concomitant steroids, *n* (%)							
Yes	454 (8.0%)	120 (8.7%)	0.411	97 (7.0%)	118 (8.6%)	0.155	0.060
No	5211 (92.0%)	1262 (91.3%)		1282 (93.0%)	1261 (91.4%)		
Concomitant immunomodulators, *n* (%)							
Yes	2046 (36.1%)	415 (30.0%)	<0.001	388 (28.1%)	415 (30.1%)	0.276	0.044
No	3619 (63.9%)	967 (70.0%)		991 (71.9%)	964 (69.9%)		

CD, Crohn's disease; PS, propensity score; SD, standard deviation; TNF, tumor necrosis factor; UST, ustekinumab.
†After PS matching using the 1:1 nearest neighbor method, 1379 patients each were included in the anti-TNF and UST groups.
‡After PS matching, covariates between the two groups were considered to be well balanced if the standardized difference was <0.1.

men (71.6%) and 2000 women (28.4%) with confirmed diagnoses of CD. The mean age at enrollment and the mean duration from a confirmed CD diagnosis were 35.6 (SD 14.6) and 3.3 (SD 5.7) years, respectively. Of the 7047 patients, 3796 (54.1%) patients started biologics within 1 year after a diagnosis of CD. Regarding previous surgery, 508 (7.2%) patients underwent surgery within 6 months of biologics initiation. Among the 7047 patients, 2620 (37.2%) patients were treated in academic hospitals, whereas 4427 (62.8%) patients were treated in non-academic hospitals. Concerning concomitant medications, 574 (8.1%) patients were treated with prednisolone, and 2461 (34.9%) patients were managed with azathioprine or 6-mercaptopurine.

When divided by the type of biologic used, the UST group had higher proportions of women, older patients, and patients treated at academic hospitals. The rate of surgery within 6 months prior to the index date was significantly higher in the UST group (12.6%) than in the anti-TNF group (5.9%). In addition, the rate of concomitant use of immunomodulators was significantly lower in the UST group (30.0%) than in the anti-TNF group (36.1%). Conversely, there was no difference in the duration from confirmed CD diagnosis to the index date or in the rate of concomitant use of steroids (Table 1).

PS matching. Multivariate logistic regression was performed to estimate the PS of each patient using the aforementioned covariates. After PS matching using the 1:1 nearest neighbor method, 1379 patients each were included in the anti-TNF and UST groups (Table 1) with a c-statistic of 0.60. There were no significant differences in clinical characteristics between the two PS-matched cohorts using a standardized difference of <0.1 for each factor.

Primary outcomes. In the anti-TNF group, 337 (24.4%) patients required treatment optimization at a mean duration of 26.3 weeks (SD 17.9). Of the 651 patients treated with IFX, 127 (19.5%) received dose increase or interval shortening; of the 728 patients treated with ADA, 210 (28.8%) received dose increase. On the other hand, in the UST group, 763 (55.3%) patients received interval shortening at a mean duration of 21.4 weeks (SD 11.3).

During a mean observation period of 41.4 weeks (SD 31.5), 281 and 273 patients required hospitalization in the anti-TNF and UST groups, respectively. The cumulative hospitalization rates in the anti-TNF and UST groups were 25.3% and 26.5% at 1 year and 33.8% and 39.8% at 2 years, respectively. There was no significant

difference in the cumulative hospitalization rates between the two groups (P = 0.849; Fig. 2). Likewise, 67 and 55 patients underwent surgery in the anti-TNF and UST groups, respectively. The cumulative surgery rates in the anti-TNF and UST groups were 5.5% and 5.1% at 1 year and 8.3% and 8.4% at 2 years, respectively. The cumulative surgery rates between the two groups were also comparable (P = 0.458; Fig. 3).

Regarding the treatment persistence rate in the anti-TNF and UST groups, the rate at 1 year was higher in the UST group (90.8% *vs* 92.5%), and that at 2 years was higher in the anti-TNF group (81.2% *vs* 74.6%); however, there was no significant difference in the cumulative persistence rate between the two groups (P = 0.549; Fig. 4).

Secondary outcomes. In 1955 (70.9%) patients without concomitant immunomodulators, there were no significant differences in the cumulative hospitalization, surgery, and persistence rates between the anti-TNF and UST groups (Fig. 5a–c). Similarly, in 803 (29.1%) patients with concomitant immunomodulators, the cumulative hospitalization, surgery, and persistence rates were not significantly different between the anti-TNF and UST groups (Fig. 5d–f). After dividing the anti-TNF group into the IFX or ADA groups, there were no significant differences in the cumulative hospitalization, surgery, and persistence rates among the IFX, ADA, and UST groups (Fig. 6a–c).

Discussion

In this large database analysis, the effectiveness of anti-TNF agents and UST were revealed to be similar in CD patients without prior use of biologics. That is, there were no differences in the hospitalization rates, surgery rates, or persistence rates (defined as discontinuation or change in biologic therapy due to exacerbation of CD) between the anti-TNF and UST groups.

Although the efficacy of biologics in patients with CD has been demonstrated in many clinical trials, most of these trials evaluated drug effectiveness in comparison to placebo. However, there have been no direct comparative studies in CD. In the absence of direct comparative studies, the selection of biologics is challenging. Therefore, a network meta-analysis indirectly compared the effects of biologics by combining placebo-controlled clinical trials.[9] In biologic-naïve patients, although the response rate was higher for IFX than for UST, there was no significant difference in the remission rate. In addition, the response and remission rates of ADA were comparable to those of UST. Since this is only an indirect comparison, large-scale direct comparative studies have been warranted.

Because UST became available after anti-TNF agents, reports of its effectiveness in patients who did not respond to anti-TNF agents have been the main focus of reports on real-world data, mainly in comparison to the effectiveness of vedolizumab, another late-breaking biologic.[18,19] In addition, it has been believed that it

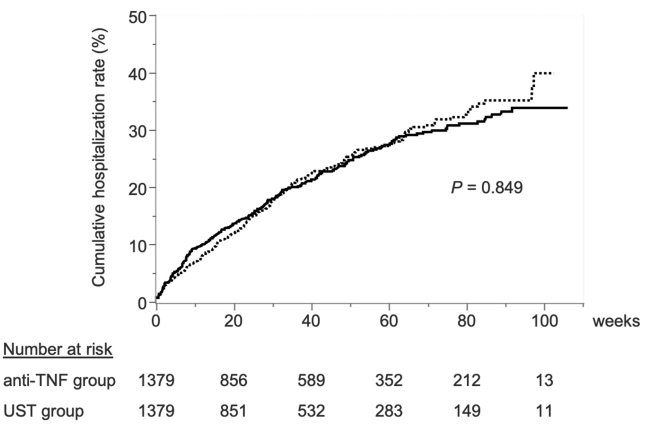


Figure 2 Cumulative hospitalization rates. The cumulative hospitalization rate in patients treated with anti-tumor necrosis factor (TNF) agents were 25.3% at 1 year and 33.8% at 2 years; that in patients treated with ustekinumab (UST) were 26.5% at 1 year and 39.8% at 2 years. There was no significant difference in the cumulative hospitalization rates between the two groups (P = 0.849). — Anti-TNF group. ····· UST group.

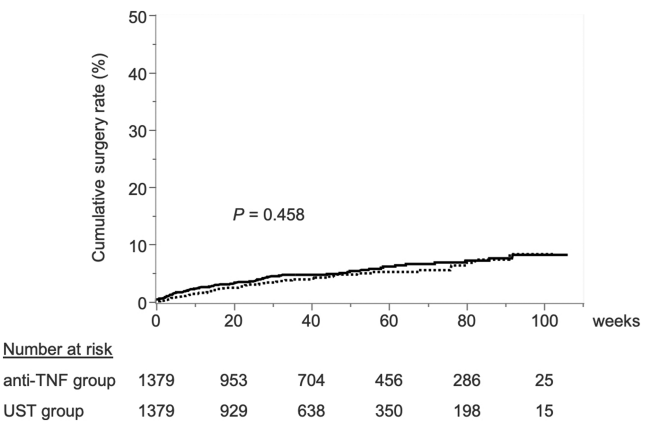
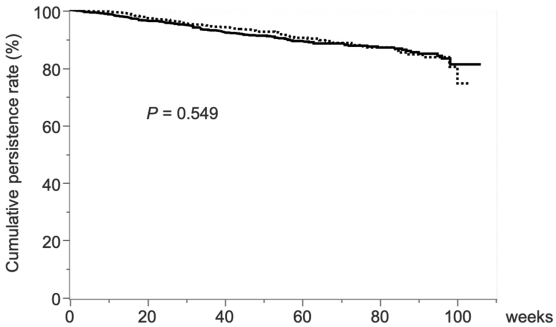


Figure 3 Cumulative surgery rates. The cumulative surgery rate in patients treated with anti–tumor necrosis factor (TNF) agents were 5.5% at 1 year and 8.3% at 2 years; that in patients treated with ustekinumab (UST) were 5.1% at 1 year and 8.4% at 2 years. The cumulative surgery rates were comparable between the two groups (P = 0.458). — Anti-TNF group. ····· UST group.



Number at risk						
anti-TNF group	1379	943	688	444	269	23
UST group	1379	925	623	337	183	14

Figure 4 Cumulative persistence rates. The treatment persistence rate at 1 year was higher in the ustekinumab (UST) group (92.5%) than in the antitumor necrosis factor (TNF) agent group (90.8%), and that at 2 years was higher in the anti-TNF agent group (81.2%) than in the UST group (74.6%); however, there was no significant difference in the cumulative persistence rates between the two groups (P = 0.549). — Anti-TNF group. ····· UST group.

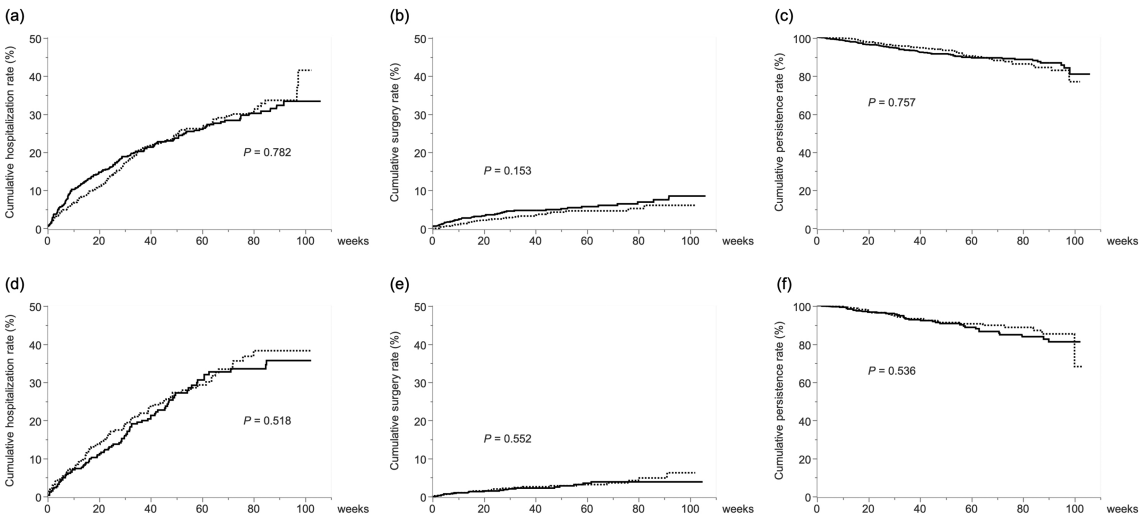


Figure 5 Cumulative hospitalization, surgery, and persistence rates analyzed separately for patients with and without immunomodulators. In 1955 (70.9%) patients without concomitant immunomodulators, there were no significant differences in the cumulative hospitalization (a), surgery (b), and persistence (c) rates between the antitumor necrosis factor (TNF) and ustekinumab (UST) groups (P = 0.782, 0.153, and 0.757, respectively). Similarly, in 803 (29.1%) patients with concomitant immunomodulators, the cumulative hospitalization (d), surgery (e), and persistence (e) rates were not significantly different between the anti-TNF and UST groups (P = 0.518, 0.552, and 0.536, respectively). — Anti-TNF group. ····· UST group.

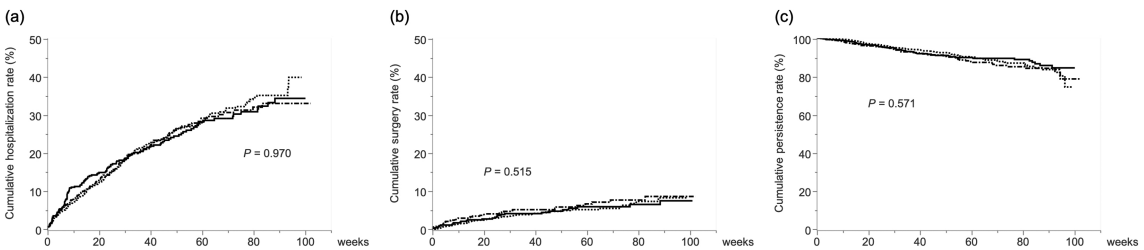


Figure 6 Cumulative hospitalization, surgery, and persistence rates analyzed dividing the anti-TNF group into the IFX and ADA groups. Dividing the anti-tumor necrosis factor (TNF) group into patients treated with infliximab (IFX) and adalimumab (ADA), we compared the treatment courses between the IFX, ADA, and ustekinumab (UST) groups. There were no significant differences in the cumulative hospitalization (a), surgery (b), and persistence (c) rates among the three groups (P = 0.970, 0.515, and 0.571, respectively). — IFX group. -·- ADA group. ····· UST group.

would take longer time for UST to exert its efficacy compared to anti-TNF agents. However, at least for biologic-naïve patients, there is a possibility that the long-term prognosis of UST may not be inferior to that of anti-TNF agents. In fact, a post hoc analysis comparing two large clinical trials in biologic-naïve CD reported equivalent efficacy between UST and IFX,[20] although it reported only on short-term outcomes. In a typical model case of CD requiring biologic treatment, the algorithm starting with UST as a first-line biologic treatment increased the remission or response rate by 10% and decreased the surgery rate by 2% at 1 year, reducing the cost of care.[21] A more recent comparative trial of ADA and UST in patients with biologic-naïve CD reported that the efficacy of ADA and UST was comparable after 52 weeks.[11–13] Throughout the present study, UST displayed comparable effectiveness to anti-TNF agents in terms of the cumulative hospitalization, surgery, and persistence rates.

Optimization of biologics (dose increase or interval shortening) is one of the most important issues in determining the effectiveness of treatment with biologics. The only comparative trial recently reported in CD showed comparable efficacy of ADA and UST; however, the issue was the unbalanced dosing of ADA, 40 mg every 2 weeks without dose adjustment, and UST, every 8 weeks instead of standard every 12 weeks.[11-13] In the present study, based on a real-world setting that included normal to adjusted doses, anti-TNF agents and UST displayed comparable effectiveness. However, detailed analysis of this real-world data revealed that a very high proportion of cases shortened their intervals to every 8 weeks from the early phases, which may also have influenced the outcomes. Another concern is that physicians may be selecting UST for patients with less severe disease. The present database analysis was not able to provide an accurate assessment of disease activity. However, intending to match the activity of both groups, we adjusted for covariates such as previous surgery within 6 months, hospital type, outpatient or inpatient status, and concomitant use of steroids.

Due to the low immunogenicity of UST, the incidence of antidrug antibodies against UST was reported to be as low as 5.8% in a long-term extension study over 5 years.[2] Considering the lower incidence of antidrug antibody production, UST does not necessarily require the concomitant use of immunomodulators, in contradiction to anti-TNF agents. In fact, large real-world data and meta-analysis have also reported that the concomitant use of immunomodulators does not improve treatment outcomes.[22,23] In the subanalysis of patients with as well as without immunomodulators, there were no significant differences in the outcomes between the anti-TNF and UST groups. As reported in the post hoc analysis of the SONIC study, it may be more important to maintain trough levels by optimizing biologic agents than to use immunomodulators in combination.[24] This may also explain why no significant differences were found between the IFX and ADA groups. In fact, according to the ECCO guidelines, the effectiveness of IFX and ADA is considered to be equivalent among anti-TNF agents.[25]

The present study had several limitations. First, the database analysis does not provide accurate information on disease activity. We performed PS matching, adjusting for various factors, to match the activity of patients treated with anti-TNF agents and UST; however, we were unable to ensure that the activity was truly equivalent. Second, as is true for any database analysis, we were unable to adjust for factors that we did not measure. For example, anal lesions, one of the major complications of CD, were not assessed in this study. Third, if we intend to evaluate long-term outcomes, a longer observation period might be required.

Database analysis based on medical claims data comparing the effectiveness of anti-TNF agents and UST revealed that these two agents had comparable long-term outcomes including hospitalization, surgery, and persistence rates for CD patients without prior use of biologics. This study might provide meaningful insight into the selection of biologic agents.

Funding

None.

Data availability statement. The data will be shared on reasonable request to the corresponding author.

References

1 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.
2 Sandborn WJ, Rebuck R, Wang Y *et al*. Five year efficacy and safety of ustekinumab treatment in Crohn's disease: The IM UNITI trial. *Clin Gastroenterol Hepatol* 2022; **20**: 578–90.e4.
3 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.
4 Iborra M, Beltrán B, Fernández-Clotet A *et al*. Real world long term effectiveness of ustekinumab in Crohn's disease results from the ENEIDA registry. *Aliment Pharmacol Ther* 2020; **52**: 1017–30.
5 Biemans VBC, 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.
6 Straatmijer T, Biemans VBC, Hoentjen F *et al*. Ustekinumab for Crohn's disease: Two year results of the initiative on Crohn and colitis (ICC) Registry, a nationwide prospective observational cohort study. *J Crohns Colitis* 2021; **15**: 1920–30.
7 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.
8 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.
9 Singh S, Fumery M, Sandborn WJ *et al*. Systematic review and network meta analysis first and second line biologic therapies for moderate severe Crohn's disease. *Aliment Pharmacol Ther* 2018; **48**: 394–409.
10 Singh S, Murad MH, Fumery M *et al*. Comparative efficacy and safety of biologic therapies for moderate to severe Crohn's disease: A systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2021; **6**: 1002–14.
11 Sands BE, Irving PM, Hoops T *et al*. 775d ustekinumab versus adalimumab for induction and maintenance therapy in moderate to severe Crohn's disease: The SEAVUE study. *Gastroenterology* 2021; **161**: e30–1.

12 Irving PM, Sands BE, Hoops T *et al*. OP02 ustekinumab versus adalimumab for induction and maintenance therapy in moderate to severe Crohn's disease: The SEAVUE study. *J Crohns Colitis* 2021; **15**: S001–2.
13 Sands BE, Irving PM, Hoops T *et al*. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic naive patients with moderately to severely active Crohn's disease: A multicentre, randomised, double blind, parallel group, phase 3b trial. *Lancet* 2022; **399**: 2200–11.
14 Yamana H, Moriwaki M, Horiguchi H *et al*. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol* 2017; **27**: 476–82.
15 Moroi R, Tarasawa K, Shiga H *et al*. Efficacy of urgent colonoscopy for colonic diverticular bleeding: A propensity score matched analysis using a nationwide database in Japan. *J Gastroenterol Hepatol* 2021; **36**: 1598–604.
16 Matsuoka K, Igarashi A, Sato N *et al*. Trends in corticosteroid prescriptions for ulcerative colitis and factors associated with long-term corticosteroid use: Analysis using Japanese claims data from 2006 to 2016. *J Crohns Colitis* 2021; **15**: 358–66.
17 Kobayashi T, Udagawa E, Uda A *et al*. Impact of immunomodulator use on treatment persistence in patients with ulcerative colitis: A claims database analysis. *J Gastroenterol Hepatol* 2020; **35**: 225–32.
18 Biemans VBC, 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; **52**: 123–34.
19 Townsend T, Razanskaite V, Dodd S *et al*. Comparative effectiveness of ustekinumab or vedolizumab after one year in 130 patients with anti-TNF refractory Crohn's disease. *Aliment Pharmacol Ther* 2020; **52**: 1341–52.
20 Narula N, Wong ECL, Dulai PS *et al*. Comparative efficacy and rapidity of action for infliximab vs ustekinumab in biologic naïve Crohn's disease. *Clin Gastroenterol Hepatol* 2022; **20**: 1579–87.e2.
21 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; **19**: 2082–92.
22 Hu A, Kotze PG, Burgevin A *et al*. Combination therapy does not improve rate of clinical or endoscopic remission in patients with inflammatory bowel diseases treated with vedolizumab or ustekinumab. *Clin Gastroenterol Hepatol* 2021; **19**: 1366–76.e2.
23 Yzet C, Diouf M, Singh S *et al*. No benefit of concomitant immunomodulator therapy on efficacy of biologics that are not tumor necrosis factor antagonists in patients with inflammatory bowel diseases: A meta-analysis. *Clin Gastroenterol Hepatol* 2021; **19**: 668–79.e8.
24 Colombel J-F, Adedokun OJ, Gasink C *et al*. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: A post hoc analysis. *Clin Gastroenterol Hepatol* 2019; **17**: 1525–32.e1.
25 Torres J, Bonovas S, Doherty G *et al*. ECCO guidelines on therapeutics in Crohn's disease: Medical treatment. *J Crohns Colitis* 2020; **14**: 4–22.