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Real-World Effectiveness and Risk Factors for Discontinuation of Ustekinumab in Ulcerative Colitis

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Keywords
Real-world evidence · Ustekinumab · Ulcerative colitis · Effectiveness · Risk factor

Abstract

Introduction: Ustekinumab (UST) has been approved for the treatment of moderate-to-severe ulcerative colitis (UC). Real-world data showing the effectiveness and safety of UST are necessary to confirm the results of clinical trials for applicability in daily clinical practice. Although some studies have reported real-world evidence of UST, only few studies have confirmed its effectiveness in the real world. The aim of this study was to assess the short- and long-term effectiveness, durability, safety, and risk factors for discontinuation of UST in UC in clinical practice. ***Methods:*** This was a retrospective, single-center, observational study. From March 2020 to January 2023, all consecutive patients with active UC who were treated with UST at Nagoya University Hospital were included. The primary outcome was the clinical remission rate at weeks 2–8 and weeks 24–48. The secondary outcomes included clinical response, persistence of UST therapy, endoscopic changes during follow-up, risk factors for UST discontinuation, and occurrence of any adverse events. The clinical effectiveness was evaluated using the Lichtiger score. ***Results:*** A total of 31 patients were included in this study. The clinical remission rates were 9.7%, 29.0%, 54.8%, and 64.5% at weeks 2, 8, 24, and 48, respectively. Twelve (38.7%) patients discontinued UST during the follow-up period. The probability of continuing UST was 93.5%, 80.6%, 77%, and 70% at weeks 2, 8, 24, and 48, respectively. The major reason for discontinuation of UST was primary failure (75.0%). A high baseline C-reactive protein (CRP) level was a significant risk factor for the discontinuation of UST. No adverse events were observed in this study. ***Conclusion:*** UST is effective for patients with UC. High CRP levels were identified as a risk factor for UST discontinuation. The findings of this study would help clinicians to select appropriate treatment options for patients with UC by identifying the risk factors for treatment discontinuation.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that causes bloody diarrhea [1]. Although advanced therapies, including anti-tumor necrosis factor (TNF) antibodies, have recently been developed and have changed the natural history of UC, some patients do not respond to first-line treatment or lose response after an initial improvement [2–4]. Ustekinumab (UST), a monoclonal antibody against the p40 subunit of the cytokines interleukin-12 and interleukin-23, has been approved for the treatment of moderate-to-severe UC based on efficacy and safety data from the UNIFI trial [5]. However, patients enrolled in randomized controlled trials do not represent those with inflammatory bowel disease observed in daily clinical practice due to the strict inclusion and exclusion criteria of clinical trials [6]. Therefore, real-world data showing the effectiveness and safety of UST are necessary to confirm the results of clinical trials for their applicability in daily clinical practice. Furthermore, the positioning of UST among other therapeutic options, such as anti-TNF antibodies, anti-integrin antibodies, and Janus kinase (JAK) inhibitors, which have also been shown to be effective in patients with UC, remains unclear [2–4]. To understand the long-term durability of response to treatment and to identify the risk factors for discontinuation of therapy, it is crucial for clinicians to select therapeutic options in their daily clinical practice. Although some studies have reported real-world evidence of UST [7–9], only few studies have confirmed the effectiveness of UST in the real world. This study aimed to evaluate the effectiveness and safety of UST in real-world settings and to identify predictors of its effectiveness. We believe that this study validates the results of clinical trials demonstrating real-world evidence of UST in patients with refractory UC, which would help clinicians to select appropriate treatment options for patients with UC by identifying the risk factors for treatment discontinuation.

Materials and Methods

Study Design

We performed a retrospective, observational study at Nagoya University Hospital between March 1, 2020, and January 1, 2023. The electronic health records were reviewed for clinical data. UST was administered intravenously at a weight-based dose (260 mg for weight <55 kg, 390 mg for weight between 55 kg and 85 kg, 520 mg for weight >85 kg) at week 0, and all patients were scheduled to receive a 90 mg dose via subcutaneous injection at week 8 after the first administration of UST. The optimization of UST therapy at a dose of 90 mg every 8 or 12 weeks was allowed for an insufficient response according to the investigator's discretion. Informed consent of the study participants was not required due to the retrospective nature of the study.

Patient Population

This study included all consecutive adult patients with UC who were treated with UST. Patients who received UST during remission or had a previous colectomy were excluded. Patients were followed-up until the last UST dose or the last visit, whichever was first.

Data Collection

Data on patient demographic and clinical characteristics, including sex, age, disease duration, disease extent, concomitant medication for UC at the beginning of and during follow-up, previous biologic agents or JAK inhibitors for UC, response to UST, clinical activity at baseline and during follow-up, date of discontinuation of UST, and adverse events, were collected. In addition, endoscopic assessments were available with the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [10] at the beginning of and during follow-up, and the results of laboratory tests, including hemoglobin, C-reactive protein (CRP), and albumin, were collected. The timing of endoscopy was decided at the clinician's discretion.

Outcome Measures

The primary outcome measure was clinical remission rate at weeks 2–8 (induction phase) and weeks 24–48 (maintenance phase). The secondary outcome measures included clinical response rates, persistence of UST therapy, endoscopic changes during follow-up, and the occurrence of any adverse events. Furthermore, risk factors associated with UST discontinuation were investigated. Clinical remission was defined as a Lichtiger score ≤3, and clinical response was defined as a Lichtiger score ≤10, with a reduction in the score of at least three points compared to before treatment [11]. Late responder was defined as the patient who achieved clinical response or remission at week 48 even though they did not achieve them at week 8. All adverse events that occurred during the UST treatment were recorded. Severe adverse events were defined as treatment interruption, hospitalization, disability, persistent damage, colectomy, or death.

Statistical Analysis

Categorical variables, expressed as numbers (%), were compared using Fisher's exact test. Quantitative variables, expressed as median (interquartile range [IQR]), were compared using the nonparametric Wilcoxon signed-rank test, as appropriate. An intention-to-treat approach in which missing data and discontinuation of UST were classified as treatment failure regardless of the reason for discontinuation was used to evaluate the effectiveness of UST, such as clinical remission and response rate.

Kaplan-Meier analysis, in which patients who discontinued UST for any reason were censored during discontinuation, was used to analyze the durability of UST. Univariate and multivariate Cox regression analyses were used to identify variables associated with UST discontinuation. According to previous studies reporting the predictors for effectiveness of UST in patients with UC [7, 8, 12], the CRP levels at baseline and previous history of vedolizumab

Table 1. Characteristics of the study population ($N = 31$)

Variables	
Age, median (IQR), years	32.0 (24.0, 45.5)
Gender, *n* (%)	
Female	12 (39)
Male	19 (61)
Median time from UC diagnosis (IQR), months	65.0 (36.0, 134.5)
Median time of follow-up (IQR), days	449.0 (196.5, 720.5)
UC extension, *n* (%)	
Extend	23 (74)
Left sided	8 (26)
Number of previous advanced therapies, *n* (%)	
0	7 (23)
1	8 (26) (ADA: 4, IFX: 2, TOF: 1, TAC: 1)
2	5 (16) (ADA+VDZ: 1, IFX+VDZ: 4)
3	5 (16) (ADA+IFX+TOF: 1, ADA+IFX+GLM: 1, IFX+GLM+VDZ: 1, IFX+GLM+TOF: 1, IFX+VDZ+TAC: 1)
4	5 (16) (ADA+IFX+GLM+TAC: 1, ADA+IFX+VDZ+TAC: 1, IFX+TOF+TAC+CsA: 1, IFX+VDZ+TOF+TAC: 1, IFX+VDZ+TOF+TAC: 1)
5	1 (3.2) (ADA+IFX+GLM+VDZ+TAC: 1)
Dose of concomitant corticosteroid, median (IQR)	2.5 (0.0, 17.5)
Concomitant immunomoderator, *n* (%)	8 (26)
Concomitant GMA, *n* (%)	4 (13)
Baseline Lichtiger score, median (IQR)	8.0 (7.0, 9.5)
Baseline UCEIS score, median (IQR)	6.0 (5.0, 6.0)
Baseline CRP, median (IQR)	0.6 (0.2, 0.9)
Baseline serum albumin, median (IQR)	3.8 (3.5, 4.0)
Previous advanced therapies	0.6 (0.2, 0.9)
IFX, *n* (%)	17 (71)
ADA, *n* (%)	10 (42)
GLM, *n* (%)	6 (25)
VDZ, *n* (%)	11 (46)
TOF, *n* (%)	6 (25)
TAC, *n* (%)	9 (38)
CsA, *n* (%)	1 (4.2)
Advanced therapies most recently administered before UST	
IFX, *n* (%)	3 (9.7)
ADA, *n* (%)	4 (13.0)
GLM, *n* (%)	3 (9.7)
VDZ, *n* (%)	5 (16.1)
TOF, *n* (%)	5 (16.1)
Median time interval between the start of UST and the last administration of advanced therapies before UST (IQR), days	28 (4, 55.5)

IQR, interquartile range; UC, ulcerative colitis; ADA, adalimumab; IFX, infliximab; TOF, tofacitinib; TAC, tacrolimus; VDZ, vedolizumab; GLM, golimumab; CsA, cyclosporine; GMA, granulocyte and monocyte adsorption; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; CRP, C-reactive protein.

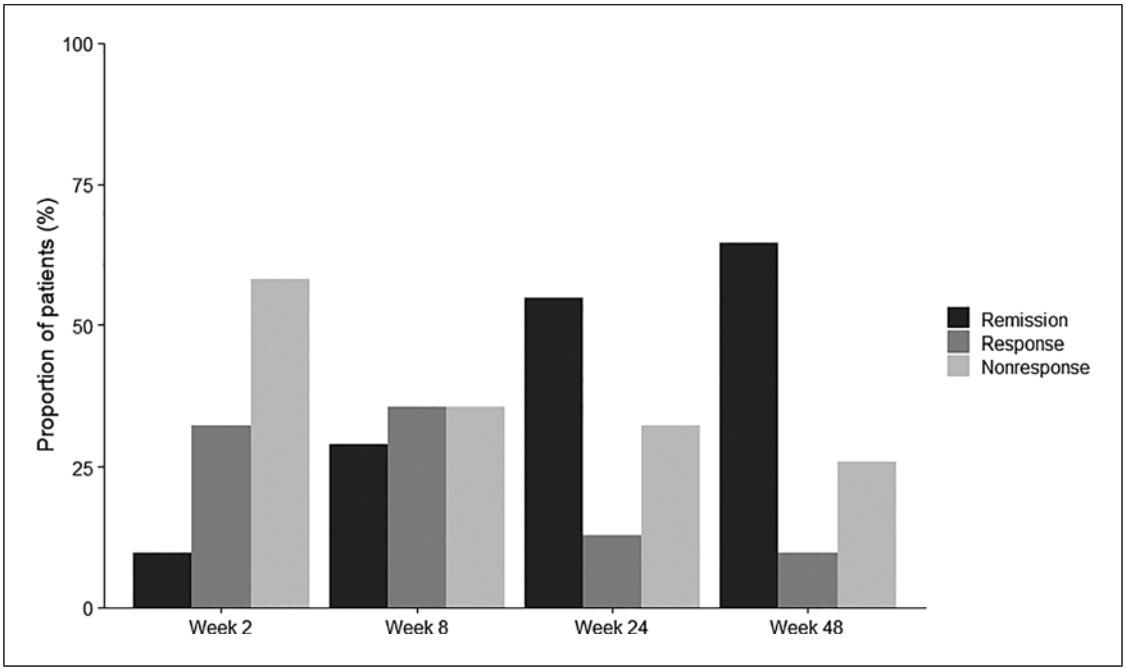

Fig. 1. Effectiveness of UST in UC.

and more than two biologic agents were used as independent variables in the multivariable Cox regression analysis in this study. Statistical significance was set at $p < 0.05$. All analyses were performed using R version 4.2.1 (Foundation for Statistical Computing, Vienna, Austria) equipped with the "survival," "survminer," "gtsummary," "janitor," and "rstatix" packages.

Results

Study Population

A total of 31 patients with UC were included in this study. The patient characteristics are listed in Table 1. The median age and time from diagnosis of UC were 32.0 (IQR: 24.0–45.5) years and 65.0 (IQR: 36.0–134.5) months, respectively. The median Lichtiger index of the patients before treatment with UST was 8.0 (IQR: 7.0–9.5). Twenty-four patients (80%) had previously been exposed to biologic agents or JAK inhibitors. A history of anti-TNFα antibody, vedolizumab, or JAK inhibitor therapy was noted in 92%, 46%, and 25% of the patients, respectively. Steroids and immunomodulators were used with UST in 51.6% and 26% of patients, respectively. Sixteen patients (52%) had been exposed to more than two biologic agents or JAK inhibitors. All patients included in this study received subcutaneous injection of UST every 8 weeks.

Treatment Effectiveness

The clinical remission and response to UST at weeks 2, 8, 24, and 48 are shown in Figure 1. Clinical remission was achieved in 3 (9.7%), 9 (29.0%), 17 (54.8%), and 20 (64.5%) patients at weeks 2, 8, 24, and 48, respectively. Of 11 patients with no response at weeks 2 or 8, 1 (9%) and 3 (27.3%) achieved clinical response and remission at week 48, respectively. Baseline CRP levels of late responders were significantly lower than those of nonresponders (Table 2). The median Lichtiger index increased from week 2 to week 48 (shown in Fig. 2). The median Lichtiger index significantly decreased from 8.0 at baseline to 4.0 between weeks 2 and 8 ($p < 0.001$). Among the 31 patients with an assessment of endoscopic activity at week 0, 29 (93.5%) endoscopic activities were re-evaluated after treatment with UST. Median time interval between the start date of UST and the date of endoscopy after the treatment of UST was 281 (IQR: 168–363) days. Endoscopic remission and response were achieved in 1 (3.5%) and 19 (65.5%) patients, respectively (shown in Fig. 3). The median UCEIS score decreased from 6 at baseline to 3 after UST treatment ($p < 0.001$).

Persistence of UST

Twelve patients discontinued treatment after a median duration of 118 (IQR: 28–325) days. The most common reason for discontinuation of UST was primary nonresponse to UST (75%, 9/12), followed by loss of response

Table 2. Comparison of clinical characteristics in nonresponders, early responders, and late responders

Variables	Early responders	Late responders	Nonresponders	*p* value
	N = 20	*N* = 4	*N* = 7	
Age, median (IQR), years	32.5 (27.0, 45.2)	35.0 (23.0, 46.8)	25.0 (24.0, 40.5)	>0.9
Gender, *n* (%)				
Female	8 (40)	1 (25)	3 (43)	>0.9
Male	12 (60)	3 (75)	4 (57)	
Median time from UC diagnosis (IQR), months	69.5 (39.8, 146.2)	31.0 (22.8, 58.5)	74.0 (41.0, 140.0)	0.4
UC extension, *n* (%)				
Extend	16 (80)	1 (25)	6 (86)	0.070
Left sided	4 (20)	3 (75)	1 (14)	
Number of previous advanced therapies, *n* (%)				
0	7 (35)	0 (0)	0 (0)	0.14
1	4 (20)	1 (25)	3 (43)	
2	3 (15)	0 (0)	2 (29)	
3	3 (15)	2 (50)	0 (0)	
4	3 (15)	1 (25)	1 (14)	
5	0 (0)	0 (0)	1 (14)	
Dose of concomitant corticosteroid, median (IQR)	3.8 (0.0, 11.2)	0.0 (0.0, 5.0)	15.0 (0.0, 20.0)	0.5
Concomitant immunomoderator, *n* (%)	5 (25)	1 (25)	2 (29)	>0.9
Concomitant GMA, *n* (%)	2 (10)	2 (50)	0 (0)	0.10
Baseline Lichtiger score, median (IQR)	8.0 (7.0, 9.2)	6.5 (5.8, 7.2)	9.0 (8.5, 10.0)	0.040
Baseline UCEIS score, median (IQR)	5.5 (5.0, 6.0)	5.5 (3.8, 7.0)	6.0 (5.5, 6.0)	>0.9
Baseline CRP, median (IQR)	0.4 (0.2, 0.6)	0.4 (0.2, 0.8)	1.1 (1.0, 1.5)	0.007
Baseline serum albumin, median (IQR)	3.8 (3.6, 4.1)	4.0 (3.8, 4.1)	3.4 (3.3, 3.7)	0.11
Infliximab, *n* (%)	10 (77)	4 (100)	3 (43)	0.2
Adalimumab, *n* (%)	5 (38)	1 (25)	4 (57)	0.6
Golimumab, *n* (%)	4 (31)	1 (25)	1 (14)	0.8
Vedolizumab, *n* (%)	5 (38)	2 (50)	4 (57)	0.9
Tofacitinib, *n* (%)	3 (23)	2 (50)	1 (14)	0.6
Tacrolimus, *n* (%)	4 (31)	1 (25)	3 (43)	0.9
Cyclosporine, *n* (%)	1 (7.7)	0 (0)	0 (0)	>0.9

IQR, interquartile range; UC, ulcerative colitis; GMA, granulocyte and monocyte adsorption; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; CRP, C-reactive protein.

(25%, 3/12). The probability of continuing UST treatment was 93.5% (95% confidence interval [CI] 85.3–100%) at week 2, 80.6% (95% CI: 67.9–95.8%) at week 8, 77.3% (95% CI: 64.0–94.0%) at week 24, and 70.0% (95% CI: 56.0–89.0%) at week 48 (shown in Fig. 4). After withdrawal of UST, 1 patient required colectomy, six received anti-TNFα antibodies, two received tofacitinib, and three received other therapeutic options. The numbers of patients who used immunomodulators with UST concomitantly were 2 (16.7%) and 6 (31.6%) in cases where UST was discontinued and continued, respectively. In the univariate and multivariate analyses, high CRP levels at baseline were found to be significantly associated with the probability of UST withdrawal (Table 3). Additionally, we explanatorily analyzed the cutoff level of CRP to predict the discontinuation of UST using the receiver operating curve. According to the receiver operating curve analysis (shown in Fig. 5), area under the curve of the CRP level at baseline was 0.86 (95% CI: 0.68–0.99). For a cutoff of 0.60, the sensitivity, specificity, positive predictive value, and negative predictive value were 78.9%, 83.3%, 78.9%, and 71.4%, respectively.

Safety

No adverse events were observed during the follow-up period.

Discussion

In this clinical practice study, we showed the real-world effectiveness of UST and its durability in patients who have failed other advanced therapies, including any biologics, such as anti-TNFα antibodies or JAK

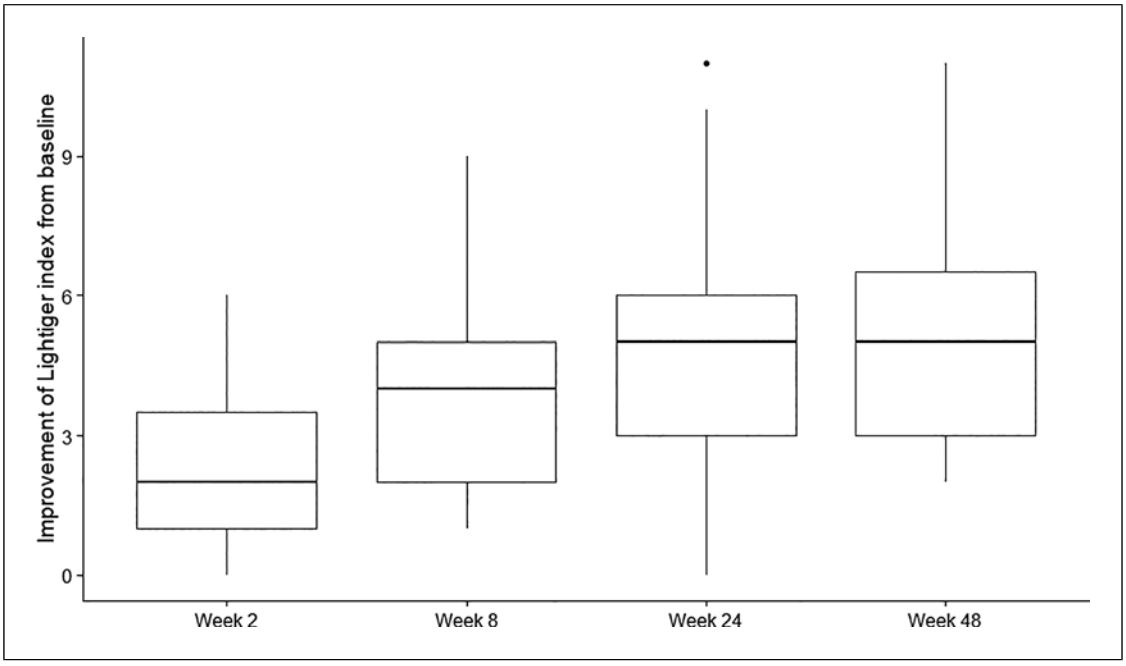

Fig. 2. Changes in the Lichtiger index score during UST therapy.

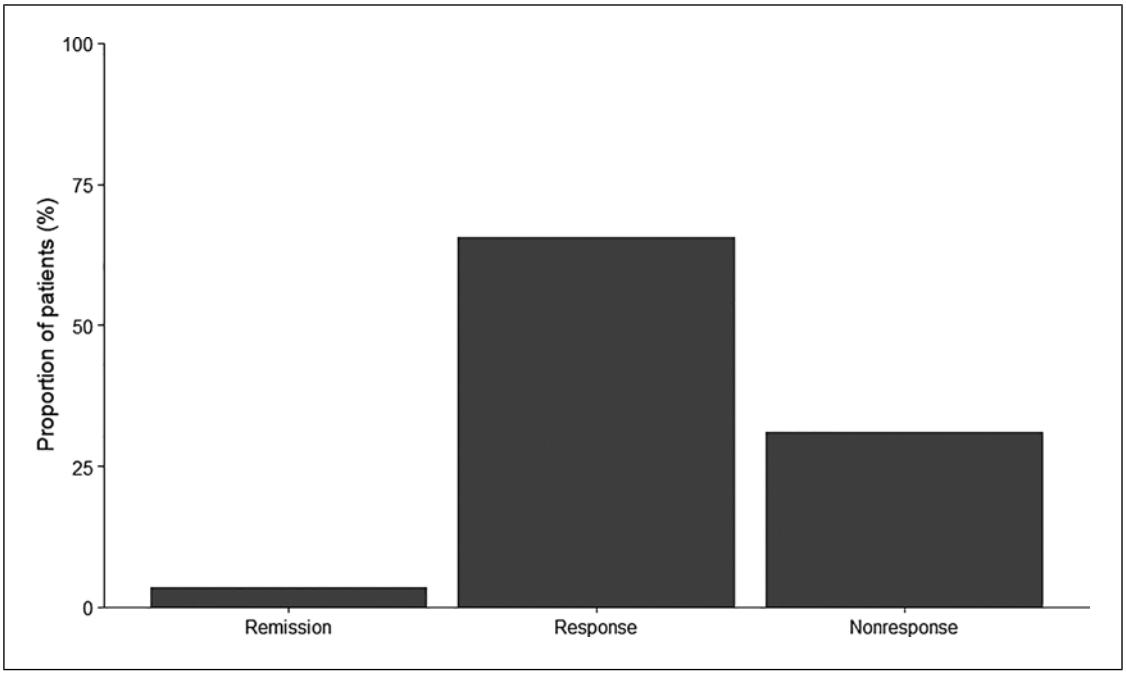

Fig. 3. Endoscopic effectiveness of UST in UC.

inhibitors. In our cohort, the rate of clinical remission was 9.7%, 29.0%, 54.8%, and 64.5% at weeks 2, 8, 24, and 48, respectively. In the UNIFI trial, which is a randomized placebo-controlled trial evaluating the efficacy and safety of UST in patients with moderate-to-severe UC at week 8 after induction therapy with intravenous UST or placebo and at week 44 for maintenance therapy after responders were randomly

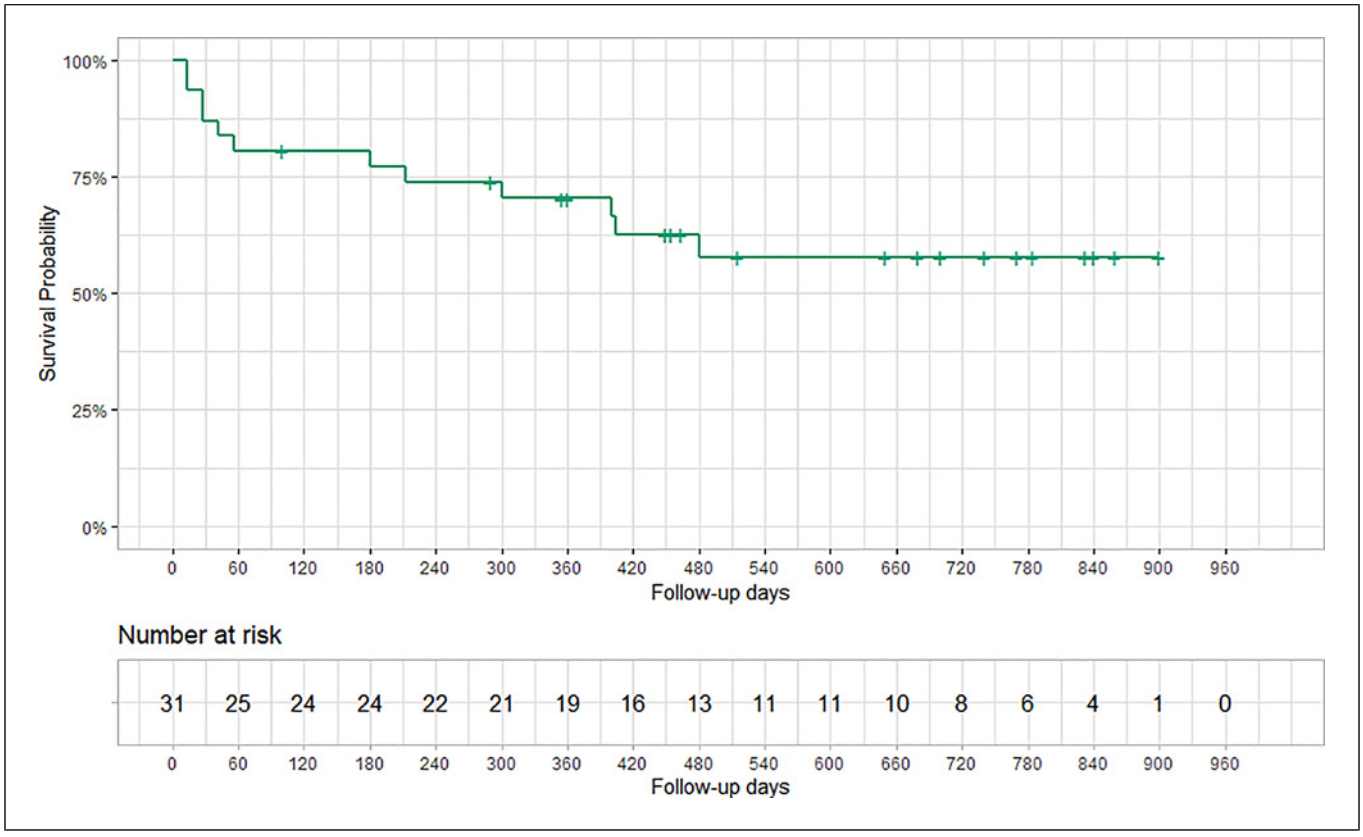

Fig. 4. Survival curve of UST treatment in UC.

Table 3. Risk factors for discontinuation of UST at 48 weeks in patients with UC

Covariates for discontinuation of UST	Univariable analysis		Multivariable analysis	
	crude HR (95% CI)	*p*	adjusted HR (95% CI)	*p* value
Prior biologic exposure >2	1.24 (0.428–3.57)	0.695		
Prior use of vedolizumab	2.81 (0.646–7.55)	0.207		
CRP at baseline	5.99 (2.46–14.6)	<0.001	7.28 (2.20–24.0)	0.00113

HR, hazard ratio; CI, confidence interval.

assigned to subcutaneous injections of UST or placebo, the percentage of patients who had achieved clinical remission at week 8 among patients who received intravenous UST at a dose of 130 mg or 6 mg per kilogram was 15.6% and 15.5%, and clinical remission at week 44 among patients assigned to subcutaneous UST treatment every 12 weeks or every 8 weeks was 38% and 44%, respectively [5]. Notably, 51.1% of the patients had previous treatment failure with biologic agents in the UNIFI study. In our cohort, 77.4% of patients had previously received any biologics, including anti-TNF, vedolizumab, and JAK inhibitors. Therefore, the long-term and short-term effectiveness of UST in this real-world study was consistent with the results reported in the UNIFI clinical trial, despite the fact that the population in our study seemed more refractory than that in the UNIFI trial. Furthermore, according to the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II, endoscopic mucosal healing is a crucial therapeutic goal of UC [13]. In our study, endoscopic remission and response were also achieved in 3.45% and 64.5% of patients, respectively.

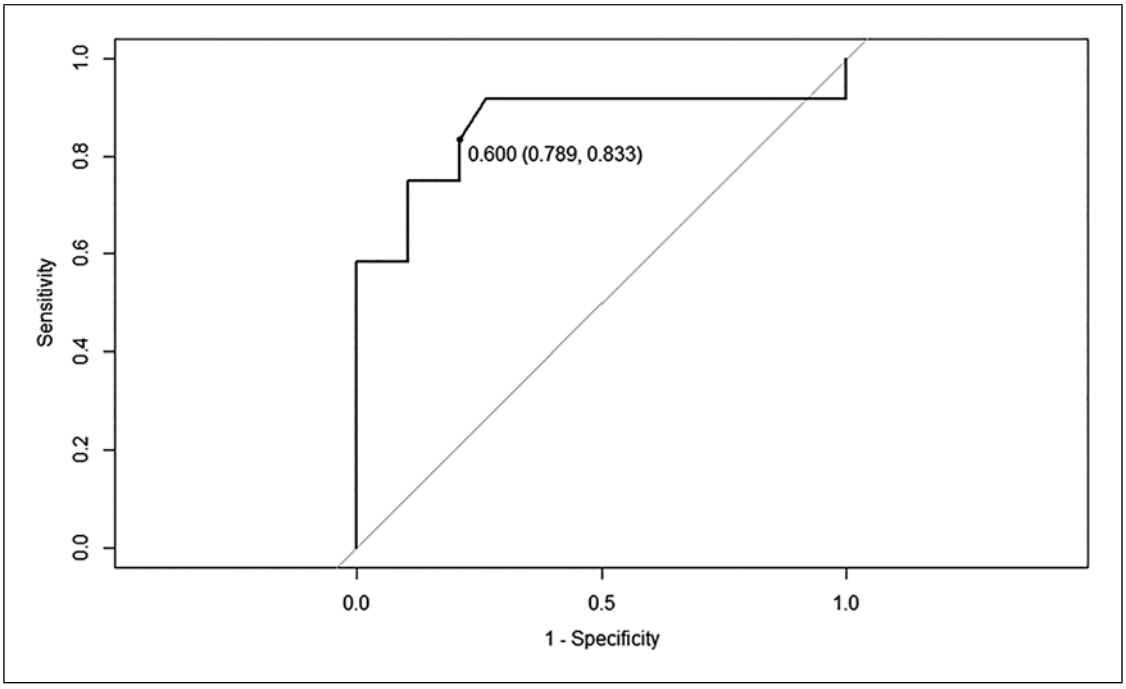

Fig. 5. Receiver operating curve of CRP levels at baseline to predict the discontinuation of UST.

Although the percentage of endoscopic remission in this study seemed to be lower than that in the UNIFI trial, in which 43.6–51.1% of patients reportedly achieved endoscopic improvement (defined as Mayo endoscopic subscore of 0 or 1) [14], bias should be considered because the timing of endoscopic evaluation in our study was not protocolized, and the definition of endoscopic improvement was different from that of the UNIFI trial. In this study, among 11 (35.5%) patients who did not show a response to UST at week 8, 4 (36.4%) patients who continued to receive UST showed a response at week 48. This result demonstrated that there were late responders to UST, congruent with the 98 (42.1%) patients who showed late response to UST in the UNIFI study. Furthermore, baseline CRP levels of late responders were significantly lower than those of nonresponders in this study. Therefore, even if patients do not respond to UST at week 8, continuing UST treatment could be a treatment option if allowed by the general condition of the patients, especially in patients with lower inflammatory burden. Regarding the durability of UST in this study, the probability of continuing UST therapy at week 48 was 70% (95% CI: 56.0–89.0%), wherein 12 (38.7%) patients discontinued the therapy. According to the survival curve of UST therapy (shown in Fig. 4), many treatment discontinuations seemed to occur within the first 60 days, and the main reason behind this was primary failure. Although 3 patients discontinued UST therapy due to secondary failure, the ability to continue the therapy seemed to be long term once the patients responded to UST. In addition, patients with a high inflammatory burden, represented by high levels of CRP [8] or partial Mayo Clinic score [7], and refractory patients with previous treatment failure to biologic agents [8] were reported to be at risk for poor outcome of UST in patients with UC in some studies. In this study, a high CRP level at baseline was associated with the discontinuation of UST at week 48, consistent with previous studies. Therefore, UST could be an effective treatment option for maintaining clinical remission over a long period, especially in patients without a high inflammatory burden of UC. No adverse events were observed in our cohort. In a systematic review of real-world data [15] and results from randomized clinical trials [5, 16], an acceptable safety profile of UST in patients with UC was reported. The results of our real-world safety data validate these results, although the number of patients included in our study was small.

Our study has some limitations. First, as this was a retrospective observational study, the results would be biased by selection and recall biases. Second, although we analyzed the risk factors for UST discontinuation, the sample size was not sufficient to obtain sufficient statistical

power to identify the risk factors. Finally, the effectiveness of UST in this study should be interpreted with caution when compared with the results of clinical trials, as the definitions of remission or response differed in each study. Nevertheless, we believe that this study validates the results of clinical trials demonstrating real-world evidence of UST in patients with refractory UC.

In conclusion, UST is effective in the induction and maintenance therapy of patients with UC in a real-world setting. More than half of the patients, including those with refractory UC, were still treated with UST at 1 year, and high CRP levels were identified as a risk factor for UST discontinuation. The findings of this study would help clinicians to select appropriate treatment options for patients with moderate-to-severe UC by identifying the risk factors for treatment discontinuation.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee at Nagoya University Hospital, approval number 2015-0466. All methods were performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki. Informed consent of the study participants was not required due to the retrospective nature of the study.

Conflict of Interest Statement

Masanao Nakamura, corresponding author has received lecture fee from Janssen Pharmaceutical K.K. There are no conflicts of interest to declare for other authors.

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None of the authors had funding sources relevant to this study.

Author Contributions

Guarantor of article: Nakamura M. Conception and design and article drafting: Uchida G. and Nakamura M. Data collection: Uchida G., Nakamura M., Yamamura T., Maeda K., Sawada T., Ishikawa E., and Furukawa K. Data analysis and interpretation: Uchida G., Iid T., Mizutani Y., Yamao K., Ishikawa T., Ishizu Y., Honda T., and Ishigami M. Critical revision of the article for important intellectual content: Kawashima H. All authors have read and approved the final version of the manuscript, including the authorship list.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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