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Observations and Research

Effectiveness and Persistency of Ustekinumab Treatment for Ulcerative Colitis: A Phoenix retrospective Cohort Study

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Background: Real-world data regarding ustekinumab (UST) for ulcerative colitis (UC) particularly in biologics-naïve patients is currently limited. This study aimed to elucidate the real-world effectiveness and safety of UST for UC.

Methods: Overall, 150 patients with UC treated with UST from March 2020 to January 2023 were enrolled across 7 referral hospitals. To assess the clinical efficacy and persistence of UST, retrospective analyses were conducted from weeks 8 to 56. Predictive factors concerning the response and persistence of UST were examined through univariate and multivariate analyses.

Results: Of the 150 patients, 125 received UST for remission induction, including 36% biologics-naïve. The response and remission rates were 72.8% and 56.0% at week 8 and 73.2% and 63.4% at week 56, respectively. Biologics-naïve patients represented higher response and remission rates at week 8 (84.4% and 73.3%) than those with biologics exposure (66.2% and 46.2%). Patients with prior antitumor necrosis factor (anti-TNF) and vedolizumab (VDZ) exposure had relatively lower response and remission rates (34.5% and 24.1%, respectively). The 1-year cumulative persistence rate was 84.0%. Multivariate analysis revealed that the chronic continuous type and prior anti-TNF and VDZ exposure were negative predictive factors for week 8 responsiveness. Clinical response at week 8 was a predictor of 1-year persistence. Adverse event incidence remained notably low at 6.4%.

Conclusions: This study highlights the safety and effectiveness of UST as an induction and maintenance therapy for UC. Chronic continuous type and previous anti-TNF and VDZ exposure negatively contributed to short-term effectiveness, whereas short-term effectiveness provided good persistency.

Lay Summary

In a retrospective analysis, the use of ustekinumab in ulcerative colitis patients was found to be effective and safe in biologics-naïve patients, whereas chronic continuous type ulcerative colitis and prior exposure to anti-TNF and vedolizumab exposure negatively contributed to short-term effectiveness.

Key Words: ulcerative colitis, ustekinumab, bio-naïve, bio-failure, persistency

Introduction

Ulcerative colitis (UC) is a refractory chronic inflammatory disorder extending to the colon and rectum. In clinical practice, patients with refractory UC, who have experienced relapse or manifested nonresponsiveness despite being treated with adequate conventional therapies (eg, 5-aminosalicylic acid [5-ASA], corticosteroids [CSs], and immunomodulators [IMs]), have received biologics and Janus kinase inhibitors (JAKis), including antitumor necrosis factor-alpha (anti-TNF-α) antibodies, vedolizumab (VDZ), and tofacitinib (TOF).[1,2] Nevertheless, the rates of remission induction associated with biologics and JAKis have been reported to

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What is already known?

Some studies regarding the clinical effectiveness of ustekinumab for ulcerative colitis (UC) with biologics exposure have already been published in western countries.

What is new here?

Ustekinumab is effective for UC with biologics-naïve as well as biologics exposure.

Chronic continuous type and previous anti-TNF and VDZ exposure negatively contributed to short-term effectiveness.

The short-term effectiveness of ustekinumab provides good persistence.

How can this study help patient care?

Our findings contribute to the establishment of an appropriate therapeutic strategy with ustekinumab for refractory UC.

hover approximately 20%–40% across various clinical trials.[2–5] Furthermore, a subpopulation of patients inevitably discontinues biologics and JAKi therapy owing to primary and secondary nonresponsiveness[6,7] and severe adverse events.[8,9] Ustekinumab (UST) constitutes a monoclonal antibody targeting the p40 subunit of interleukin (IL)-12 and -23, which is characterized as having a different mode of action from anti-TNF, VDZ, and JAKis. The UNIFI trial reported the rate of inducing and maintaining remission in the group with UST compared with that with placebo in UC with biologics failure/intolerance (bio-failure) and biologics-naïve (bio-naïve).[10] In addition, the UNIFI trial has shown a good safety profile. UST first became available for Crohn's disease in 2017 and subsequently for UC in 2020 within the clinical setting. Some studies regarding the real-world effectiveness of UST for UC have been recently published in western countries.[11–15] However, almost all cases in these studies were UC patients with biologics failure or experienced patients. Consequently, the effectiveness of UST for UC with bio-naïve in clinical practice remains unclear. Moreover, the appropriate positioning and selection strategy of UST for refractory UC with bio-naïve and bio-failure has not been fully elucidated. A principal research in the Hokkaido Organization Emphasizing Nutritional and Therapeutic Improvement to IBD Patients' Expectation (Phoenix cohort) study group has previously revealed clinical effectiveness and its predictive factors regarding UST in CD[16] in addition to anti-TNF-α antibodies (infliximab biosimilar and golimumab) in UC and CD.[17,18] In this study, using our cohort, we aimed to reveal the clinical effectiveness, remission, persistency, predictive factors associated with effectiveness and persistency, and safety of UST for inducing and maintaining UC remission, thereby contributing to elucidating the appropriate positioning of UST for UC with bio-naïve and bio-failure.

Methods

Study Population

This study constituted a multicenter observational retrospective cohort study conducted in 7 institutions constituting the principal research in the Hokkaido Organization Emphasizing Nutritional and Therapeutic Improvement to IBD Patients' Expectation (Phoenix cohort) study group in Hokkaido, Japan. Sapporo Medical University Hospital, Asahikawa Medical University Hospital, Hokkaido University Hospital, Sapporo Higashi Tokushukai Hospital, Sapporo Tokushukai Hospital, Sapporo Kosei General Hospital, and Sapporo IBD Clinic were the participating institutions. A total of 150 individuals diagnosed with UC who received UST treatment within these 7 institutions from March 2020 to January 2023 were included in this study.

The study protocol was approved by the ethics committees of the Sapporo Medical University School of Medicine (registry number: 302-101) and was similarly approved by each participating institution. This study was registered with the University Hospital Medical Information Network Center (UMIN000035384). Informed consent was obtained by announcing this study on the web and providing an opportunity to opt-out.

Data Collection

The following patient characteristics and past and concomitant medical therapy at UST induction were collected from the patient's medical records: age, sex, height, body weight, body mass index, type of UC (disease extension and clinical course), disease duration until UST induction, smoking history, presence or absence of extraintestinal manifestation, disease activity based on the Mayo score (clinical activity, partial Mayo score [pMayo] and endoscopic activity, and mayo endoscopic subscore), previous use of biologics (anti-TNF-α antibody and VDZ) and JAKis (TOF) before UST induction, and concomitant therapy at UST induction (5-ASA, CSs [systemic and topical administrations], IMs, tacrolimus [Tac], and cytapheresis [granulocyte and monocyte apheresis {GMA}]). The following were the reasons for UST induction: 5-ASA/IM refractory, steroid-dependent, steroid-resistant, primary nonresponse to biologics/Tac, secondary nonresponse to biologics, switching from Tac, and intolerance to conventional therapy (5-ASA, IM, and CS). The investigators were tasked with selecting the 2 primary reasons for initiating UST therapy. The following laboratory data were collected from medical records before and after UST induction: White blood cell count, hemoglobin (Hb), serum albumin (Alb), C-reactive protein (CRP), leucine-rich α2 glycoprotein (LRG), and fecal calprotectin. In addition, the clinical and endoscopic activity, therapeutic response to UST, presence or absence of additional or altered therapy (including colectomy), the dosing interval of UST administration during the maintenance phase (every 8 or 12 weeks), persistency of UST, and adverse events following UST induction at weeks 2, 4, 8, 16, 32, and 56 were collected from medical records.

Outcomes and Definitions

Based on the definition in the UNIFI trial,[10,19] clinical remission was defined as a pMayo score of 2 points or lower, coupled with a stool score of 0 or 1 and a rectal bleeding score of 0 in this study. Clinical improvement was defined as an improvement in the pMayo score by a minimum of 3 points and an improvement of at least 30% following UST induction. CS-free remission was defined as clinical remission with CS discontinuation or without CS addition at observational points. Clinical response was defined as clinical remission plus clinical improvement. In evaluating the effectiveness of UST, responders to UST were regarded as patients who

met the definition of clinical response and remission at the observational periods without additional therapy following UST induction. Nonresponders to UST were classified into the following corresponding patients: (1) patients who failed to achieve clinical response following UST induction regardless of the presence or absence of additional therapy and (2) patients who received additional therapy following UST induction for judgment of insufficient response to UST alone until observational periods and subsequently achieved clinical response. The patients with discontinuation of UST due to nonresponse to UST until each observational period were calculated as nonresponders at each observational point. Additional therapy involved a new prescription and/or an increasing dose (or interval) of CS (systemic or topical), IM, Tac, and GMA in the situation where UST was continued until observational points.

When missing data at observational points existed owing to an unachieved observational period or disruption, the cases were excluded from the analysis of clinical effectiveness and were considered censored at the points. In this study, the allowance at each observational point was set as follows; within 1 week before and after week 8 or 16, and within 2 weeks before and after week 32 or 56.

The following were the study endpoints: (1) clinical remission (including CS-free remission) and response rate in the induction (weeks 8 and 16) and maintenance (weeks 32 and 56) phases among all patients with UC who received UST, including those with or without prior biologics and JAKi exposure; (2) temporal alteration of pMayo and laboratory data; (3) predictive factors associated with response to UST at week 8; (4) persistence of UST and predictive factors associated with persistence of UST; and (5) adverse events occurring following UST induction.

Evaluation of the Persistence of UST

In evaluating the factors associated with the persistence of UST, patients who received additional therapy following UST induction for judgment of insufficient response to UST alone until observational periods and subsequently achieved clinical response at week 8 in addition to responders to UST alone were regarded as "responder with or without additional therapy." Responders with or without additional therapy at week 8 and responders to UST alone at week 8 were examined as covariates in the univariate and multivariate analyses regarding the factors associated with UST persistence.

Statistical Analyses

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Australia). To assess the distinctions between variables among patients with and without a response to and persistence of UST, the univariate analysis involved the application of the unpaired *t*-test and Fisher's exact test. In the multivariate analysis, the factors associated with response were analyzed using a logistic regression model. Covariates that demonstrated significance in the univariate analysis were subsequently integrated into the logistic regression model. The cumulative persistence rate of UST was calculated using the Kaplan–Meier method, with comparisons made among various groups using a log-rank test. Bonferroni correction was applied in cases involving comparison among more than 3 groups. The factors associated with persistency were analyzed using a Cox proportional hazards model, which included parameters that were identified as significant in a log-rank test. P values of $< .05$ were considered statistically significant.

Results

Patients' Characteristics

The characteristics of the 150 patients with UC who received UST are summarized in Supplementary Table S1. Within this cohort, 125 patients received UST for the induction of remission in the state of pMayo 3 or higher. In contrast, 23 patients exhibiting a pMayo score of 2 or lower received UST as maintenance therapy. Two additional patients received UST to manage pouchitis following colectomy. In this study, the analysis of clinical effectiveness and persistency was focused on 125 patients who received UST for the induction of remission. The baseline characteristics of the 125 patients are shown in Table 1. The average age at UST induction was 42.8 years, and 59.2% were male (74/125). The average disease duration until UST induction was 75.0 months. The disease extent among these patients was pancolitis type (E3), accounting for 85.6%. Regarding the clinical course, the proportion of relapse-remitting type and chronic continuous type was 74.6% and 22.4%, respectively. Furthermore, 70.4% were classified as steroid-dependent, whereas 8.8% were steroid-resistant. The average pMayo score at the onset of UST treatment was 5.8 points. Regarding prior therapy, 36.0% of the patients were categorized as bio-naïve, whereas 58.4% had previously received anti-TNF-α antibody treatment. Furthermore, 29.6% had previous experience with VDZ, and 12.0% had been exposed to TOF. Among the patients, 25.6% had previously received a single biologic or TOF, and 38.4% had received 2 or more agents. Moreover, 23.2% had previously received both anti-TNF-α antibody and VDZ. All patients with previous TOF exposure had a history of receiving anti-TNF-α antibodies and/or VDZ before TOF administration. At UST treatment initiation, 33.6%, 38.4%, 5.6%, and 8.0% of the patients were concurrently receiving prednisolone (systemic administration), azathiopurine and 6-mercaptopurine, tacrolimus, and GMA, respectively.

Reasons for UST Induction

The reasons for UST induction comprised 41.0% being steroid-dependent, followed by 20.7% being secondary nonresponders to biologics, 10.3% being primary nonresponders to biologics and/or Tac, 8.8% being intolerant to previous therapies, 7.7% being 5-ASA/IM refractory, 5.0% being steroid-resistant, 2.3% who switched from Tac, and 4.1% being others.

The top 3 combinations of the reasons for UST induction included 23.0% steroid-dependent plus secondary nonresponse to biologics, 14.0% steroid-dependent alone, and 12.0% steroid-dependent plus primary nonresponse to biologics/Tac.

Clinical Effectiveness of UST in Inducing and Maintaining Remission for UC

This study included 125, 121, 99, and 82 patients at weeks 8, 16, 32, and 56, respectively. The clinical response and remission rates in the overall population were 72.8% (91/125) and 56.0% (70/125), 71.1% (86/121) and 53.7% (65/121),

Table 1. Characteristics of patients who received ustekinumab for remission induction.

	N = 125
Age (years)	42.8 ± 16.5
Sex (male/female)	74/51
Body weight (kg)	60.2 ± 11.3
BMI (kg/m^2)	22.1 ± 3.6
Disease duration (months)	75.0 ± 98.6
Type of disease (disease extent; *n*, %)	
E1	3 (2.4)
E2	15 (12.0)
E3	107 (85.6)
Type of disease (clinical course; *n*, %)	
Relapse-remitting type	94 (74.6)
Chronic continuous type	28 (22.4)
Steroid-dependent (*n*, %)	88 (70.4)
Steroid-resistant (*n*, %)	11 (8.8)
Smoking history (none/current/past)	77/9/38
pMayo score at induction	5.8 ± 1.6
MES at induction (*n* = 93; 0/1/2/3)	2.5 ± 0.5 (0/2/42/53)
Hb level at induction (g/dl)	12.3 ± 1.9
Alb level at induction (g/dL)	3.77 ± 0.61
CRP level at induction (mg/dL)	1.19 ± 2.10
Concomitant therapy at induction (*n*, %)	
5-ASA	78 (62.4)
Prednisolone	42 (33.6)
Topical steroiod	19 (15.2)
Azathiopurine/6-mercaptopurine	48 (38.4)
Tacrolimus	7 (5.6)
GMA	11 (8.0)
Preceding biologics and JAKis before UST induction (*n*, %)	
None	45 (36.0)
Anti-TNF-α antibody	50 (40.0)
VDZ	24 (19.2)
TOF	6 (4.8)
Previous use of biologics and JAKis (*n*, %)	
None (biologics-naïve)	45 (36.0)
Anti-TNF-α antibody	73 (58.4)
VDZ	37 (29.6)
TOF	15 (12.0)
Others	3 (2.4)
Number of biologics and JAKis previously used (0/1/2/3/4/5)	45/32/32/9/4/3
Anti-TNF-α antibody alone (*n*, %)	42 (33.6)
VDZ alone (*n*, %)	8 (6.4)
Anti-TNF-α antibody + VDZ (*n*, %)	29 (23.2)

71.7% (71/99) and 60.6% (60/99), and 73.2% (60/82) and 63.4% (52/82) at weeks 8, 16, 32, and 56, respectively (Figure 1A). In the bio-naïve group, the clinical response and remission rates were 84.4% (38/45) and 73.3% (33/45), 81.8% (36/44) and 70.4% (31/44), 81.3% (26/32) and 75.0% (24/32), and 83.3% (25/30) and 80.0% (24/30) at weeks 8, 16, 32, and 56, respectively. For the biologics failure group, the corresponding rates were 66.3% (53/80) and 46.3% (37/80), 64.9% (50/77) and 44.1% (34/77), 67.2% (45/67) and 53.7% (36/67), and 67.3% (35/52) and 53.8% (28/52) at weeks 8, 16, 32, and 56, respectively (Figure 1B). The biologics failure group had a lower clinical remission rate than the bio-naïve group. The clinical effectiveness of UST with ≥ 2 agents of previous biologics use and TOF was equivalent to that with one agent of previous biologics use and TOF (Figure 1C). At weeks 16 and 56, the CS-free remission rates in the overall population were 47.9% (58/121) and 58.5% (48/82), respectively (Figure 2A). In the classification of Bio/TOF experience, the CS-free remission rates at weeks 16 and 56 in the bio-naïve group were 70.5% (30/44) and 76.7% (23/30), respectively, whereas those in the biologics failure group were 36.3% (28/77) and 48.1% (25/52), respectively (Figure 2B). At week 8, the clinical response and remission rates in the group with previous use of both anti-TNF and VDZ were 34.4% and 24.1%, respectively, which were lower than those in the groups with previous use of anti-TNF alone (85.7% and 57.1%), VDZ alone (87.5% and 75.0%), and TOF (80.0% and 60.0%; Figure 3). Similarly, at weeks 16, 32, and 56, the clinical remission rate with previous use of both anti-TNF and VDZ was lower than that in the other 3 groups (Supplementary Figure S1). Of the 34 patients with nonresponse to UST alone until week 8, 13 received additional therapy, and 8 of the 13 patients had a history of both anti-TNF and VDZ. At week 8, 7 patients achieved clinical response (5 with clinical remission and 2 with clinical improvement) by receiving additional therapy (5 of CS and 2 of Tac), whereas 6 were nonresponders despite receiving additional therapy (5 of CS and 1 of GMA). In this cohort, regarding the interval of UST administration (every 8 or 12 weeks) among the 109 patients treated at weeks 16–20, 87.2% (95/109) received UST every 8 weeks and 12.8% (14/95) every 12 weeks. The proportion of the patients with bio-naïve was 38.9% (37/95) in the group with every 8 weeks and 28.5% (4/14) in the group with every 12 weeks. In the group with every 8 weeks of subcutaneous UST, the clinical response and remission rates were 80.8% (59/73) and 68.5% (50/73) at week 32, and 85.0% (51/60) and 75.0% (45/60) at week 56, respectively. In the group with every 12 weeks of subcutaneous UST, the clinical response and remission rates were 78.6% (11/14) and 71.4% (10/14) at week 32, and 80% (8/10) and 70% (7/10) at week 56, respectively (Supplementary Figure S4). There was no significant difference between the groups with 8- and 12-week intervals. Interval of administration of UST were modified to every 12 weeks during UST therapy in 6 cases of 95 patients (6.3%) with every 8 weeks, while the interval of administration of UST were modified to every 8 weeks during UST therapy in 5 cases of 14 patients (35.7%) with every 12 weeks.

Temporal Changes in Clinical Symptoms and Laboratory Data

The changes in pMayo scores and laboratory data associated with UC activity (Hb, Alb, and CRP) between responders and nonresponders at week 8 were compared at baseline and at weeks 2, 4, 8, and 16. The average of pMayo scores at baseline was almost equivalent between the 2 groups (5.8 and 5.4 points in responders and nonresponders, respectively). Even at week 2, the average of pMayo scores in responders (3.4 points) was significantly lower than that in nonresponders

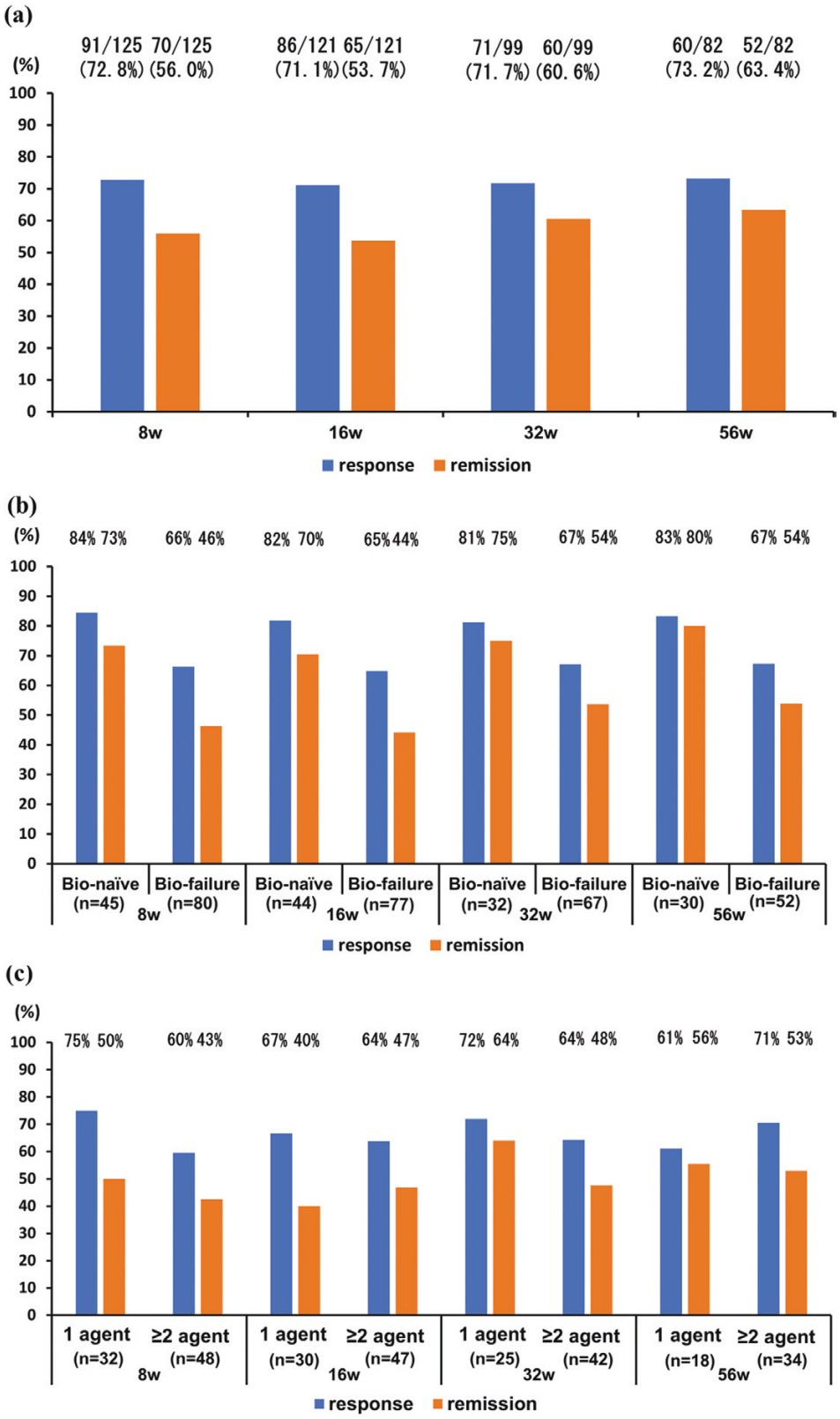

Figure 1. Clinical response and remission rates of ustekinumab (UST) for ulcerative colitis (UC) in overall population (A) at weeks 8, 16, 32, and 56, and in the (B) classification with previous use of biologics and Janus kinase inhibitors (JAKs; biologics [bio]-naïve/bio-failure) and (C) classification with the number of previous use of biologic agents (bio 1 agent/bio ≥ 2 agents).

(4.8 points; $P = .01$; Supplementary Figure S2). At week 2, the average of pMayo scores decreased from 5.8 at baseline to 3.4 (– 2.4) points in the response group and 5.4 at baseline to 4.8 (– 1.0) points in the nonresponse group ($P = .01$). The difference in pMayo scores between the 2 groups further spread until week 8. At any point, changes in Hb, Alb, and CRP

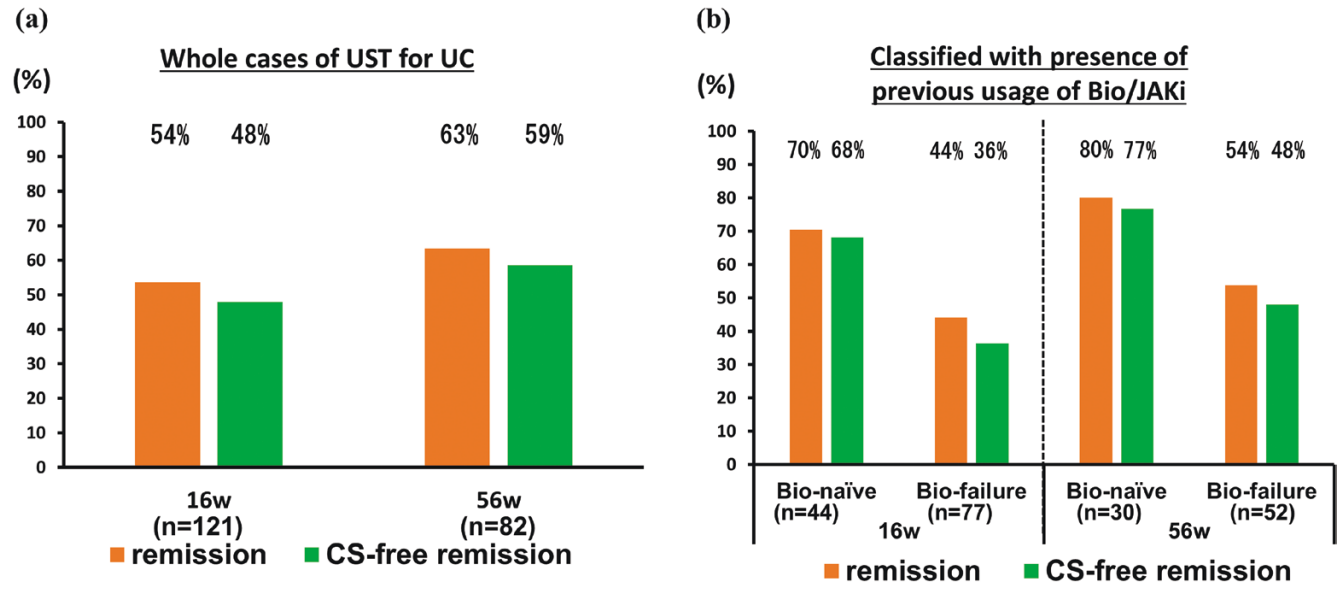

Figure 2. Corticosteroid (CS)-free clinical remission rate of UST for UC at weeks 8, 16, 32, and 56 in the (A) overall population and (B) classification with previous use of biologics and JAKis (bio-naïve/bio-failure). (The clinical remission rate as control is shown on the left side).

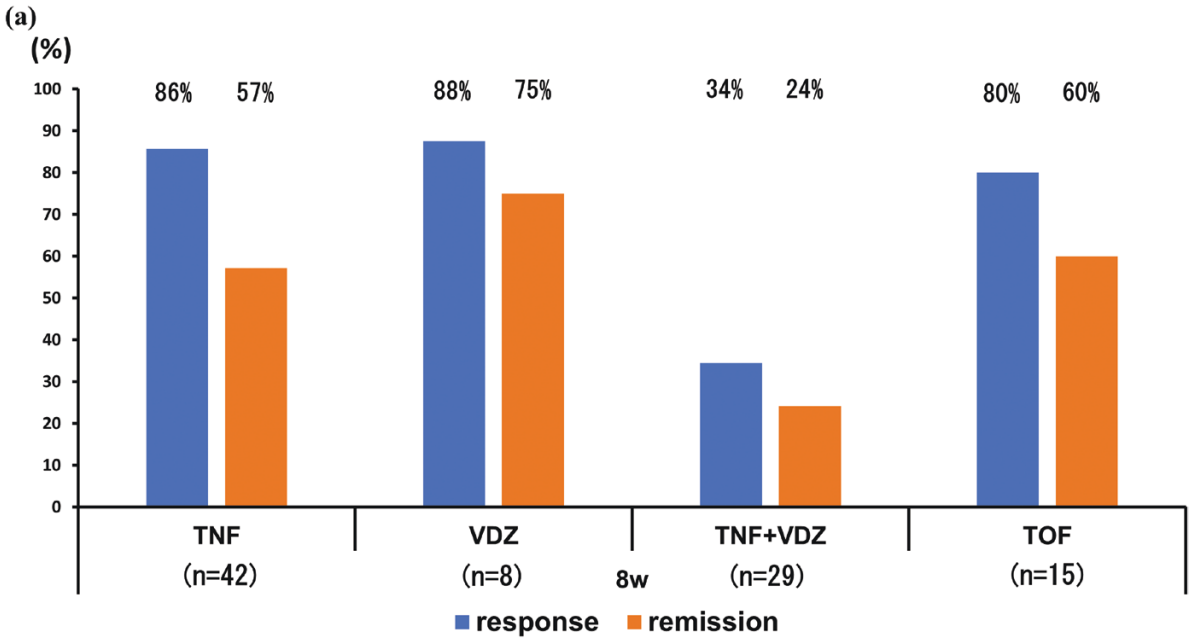

Figure 3. Clinical response and remission rates of UST for UC at week 8 in the classification with previous use of antitumor necrosis factor (anti-TNF), vedolizumab (VDZ), and tofacitinib (TOF).

levels were not significant between the 2 groups in responders and nonresponders at week 8, whereas the average CRP level at baseline in responders (1.78 mg/dl) was lower than that in nonresponders (1.03 mg/dl; $P = .127$; Supplementary Figures S3A–C).

Predictive Factors Associated With Response to UST at Week 8

Variables between the response (R) and nonresponse (non-R) groups were compared using univariate and multivariate analyses to identify factors associated with response to UST at week 8. In the univariate analysis (Table 2), disease extent of pancolitis (E3), chronic continuous type, CRP ≥ 0.28 at induction, previous use of Bio/JAKi, and previous use of anti-TNF + VDZ were significant negative predictive factors correlated with response to UST at week 8. Additionally, concomitant 5-ASA and previous use of anti-TNF alone were significant positive predictive factors for response to UST at week 8. In the multivariate analysis using a logistic regression model (Table 3), chronic continuous type (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.070–0.079; $P = .0192$) and previous use of anti-TNF and VDZ (OR, 0.085; 95% CI, 0.010–0.22; $P = .021$) were the negative predictive factors for response to UST.

Table 2. Predictive factors of response to ustekinumab for UC at week 8 in univariate analysis.

	Response (*n* = 91)	Nonresponse (*n* = 34)	*P*-value
Age (years)	43.3	41.5	.573
Sex (male/female)	54/37	20/14	1
Disease duration (months)	69.8	87.1	.368
BMI	22.2	22.0	.765
Smoking history	35 (38.4)	12 (35.3)	.953
Disease extent of E3 (*n*, %)	74 (81.3)	33 (97.1)	.0241
Chronic continuous type (*n*, %)	13 (14.2)	15 (44.1)	.0012
Steroid-dependent (*n*, %)	64 (70.3)	24 (70.6)	1
Steroid-resistant (*n*, %)	9 (9.9)	2 (5.9)	.726
pMayo score at induction	5.81	5.91	.486
Hb level at induction (g/dl)	12.3	12.2	.638
Alb level at induction (g/dL)	3.81	3.65	.193
CRP level at induction (mg/dL)	0.98	1.71	.083
CRP level at induction ≥ 0.28 (*n*, %)	42 (46.2)	23 (67.6)	.044
MES at induction	2.54	2.48	.620
Concomitant 5-ASA (*n*, %)	61 (67.0)	16 (47.1)	.0159
Concomitant IM (*n*, %)	32 (35.1)	16 (47.1)	.301
Concomitant PSL (*n*, %)	29 (31.9)	13 (38.2)	.528
Bio-naive (*n*, %)	38 (41.8)	7 (20.6)	.036
Bio-exposure (*n*, %)	53 (58.2)	27 (79.4)	
Number of previous use of bio/JAKis (*n*, %)			.689
1	24 (26.3)	8 (23.5)	
≥2	29 (31.9)	19 (55.8)	
Anti-TNF alone (*n*, %)	36 (41.8)	6 (17.6)	.032
VDZ alone (*n*, %)	7 (7.7)	1 (2.9)	.445
Anti-TNF + VDZ (*n*, %)	10 (11.0)	19 (55.8)	<.0001
TOF (*n*, %)	12 (13.1)	3 (8.8)	.758
Tac/bio primary nonresponse (*n*, %)	15 (16.5)	9 (26.5)	.213
Bio secondary nonresponse (*n*, %)	34 (37.4)	15 (44.1)	.540

Persistent UST for UC and its Related Factors

The persistence rates of UST at 6 and 12 months were 87.8% and 84.0%, respectively (Figure 4A). The average observational period for the overall population was 340 days. Discontinuation in all 21 cases occurred owing to nonresponse to UST treatment, with no cases attributed to adverse events. Three patients underwent colectomy due to nonresponse to UST treatment during the observational period. In the comparison of UST persistence among with or without clinical response at week 8, we focused on whether responsiveness to additional therapy in nonresponders to UST alone influenced UST persistence. Therefore, in evaluating UST persistence, responders with or without additional therapy at week 8 as well as responders to UST alone at week 8 were examined as covariates in the univariate and multivariate analyses. The cumulative 1-year persistence of UST in responders to UST alone (91.6%) was significantly higher than that in nonresponders (66.7%; $P < .001$). The 1-year persistence of UST in responders to UST with or without additional therapy at week 8 (91.1%) was significantly higher than that in nonresponders to UST with or without additional therapy (58.3%; $P < .001$; Figure 4B). Furthermore, the 1-year persistence of UST in the group with previous use of anti-TNF and VDZ (64.2%) was significantly lower than that in the groups with bio-naïve patients (93.4%) and previous use of anti-TNF or VDZ alone (87.6%; $P = .0049$, 0.043, respectively; Figure 4B). The 1-year persistence of UST in the classification with previous exposure to biologics (bio-naïve, 93.3%; bio-failure, 63.3%; $P = .036$) and that with previous exposure to both anti-TNF and VDZ (non-TNF and VDZ, 90.3%; both TNF and VDZ, 64.2%; $P = .036$) are shown in Figures 4C and D. The factors associated with 1-year persistence of UST, as determined by univariate analysis, are summarized in Table 4. In the multivariate analysis using a Cox regression model, the response to UST with or without additional therapy at week 8 was the only independent factor associated with UST persistence (OR, 8.19; 95% CI, 1.06–63.45; $P = .0439$; Table 5).

Adverse Events During UST Therapy

The overall proportion of patients with adverse events was low at 6.4% (8/125). Pulmonary embolism ($n = 1$), arthritis ($n = 1$), paranasal sinusitis and coronavirus disease 2019 ($n = 1$), fatigue and headache ($n = 1$), herpes zoster ($n = 1$), infectious colitis ($n = 1$), cytomegalovirus colitis ($n = 1$), and pneumocystis pneumonia ($n = 1$) were the adverse events noted. No new safety signal was observed in this cohort.

Discussion

The present study demonstrated that UST was effective and safe for inducing and maintaining remission of UC with both bio-naïve and bio-failure based on a real-world retrospective multicenter cohort (Phoenix cohort)[16–18] in Japan. Most patients had bio-failure in previous real-world studies conducted in western countries[11–13]; therefore, the real-world effectiveness of UST for patients with bio-naïve UC remains unclear. This study demonstrated the real-world effectiveness of UST for patients with bio-naïve UC. We observed that previous use of both anti-TNF and VDZ and the chronic continuous type were negatively associated with the response to UST therapy in patients with UC. Furthermore, we noted that the 1-year persistency of UST was over 80% without discontinuing cases due to adverse events. The response to UST at week 8 was the factor contributing to 1-year UST persistence. The proportion of adverse events was 6.4%, suggesting that the safety profile in this cohort was similar to that of the UNIFI trial.[10]

Cytokines produced by the Th1 and Th17 pathways have been demonstrated to strongly contribute to UC pathophysiology.[20] IL-12 is required for Th1 cell differentiation, and IL-23 is required for Th17 cell proliferation and maintenance. Moreover, UST, a monoclonal antibody targeting the p40 subunit, which constitutes both IL-12 and IL-23, is suggested to control chronic inflammation in UC by blocking the Th1 and Th17 pathways induced by IL-12 and IL-23. According to the current network meta-analysis from clinical trials, the clinical response and remission rates of biologics and JAKis

Table 3. Predictive factors of response to ustekinumab for UC at week 8 in multivariate analysis.

	Univariate analysis*			Multivariate analysis**	
	R ($n = 91$)	Non-R ($n = 34$)	*P*-value	OR (95% CI)	*P*-value
Disease extent of E3	74 (81.3)	33 (97.1)	.0241	2.9 (0.34–25.0)	.328
Chronic continuous type	13 (14.2)	15 (44.1)	.0012	0.24 (0.07–0.79)	.0192
Concomitant 5-ASA	61 (67.0)	16 (47.1)	.0159	0.98 (0.34–2.78)	.960
Bio-naive	38 (41.8)	7 (20.6)	.036	1.11 (0.15–8.43)	.922
Anti-TNF alone	36 (41.8)	6 (17.6)	.032	1.62 (0.22–11.1)	.629
Anti-TNF + VDZ	10 (11.0)	19 (55.8)	<.0001	0.085 (0.010–0.22)	.021
CRP ≥ 0.28	42 (46.2)	23 (67.6)	.044	0.47 (0.47–5.88)	.146

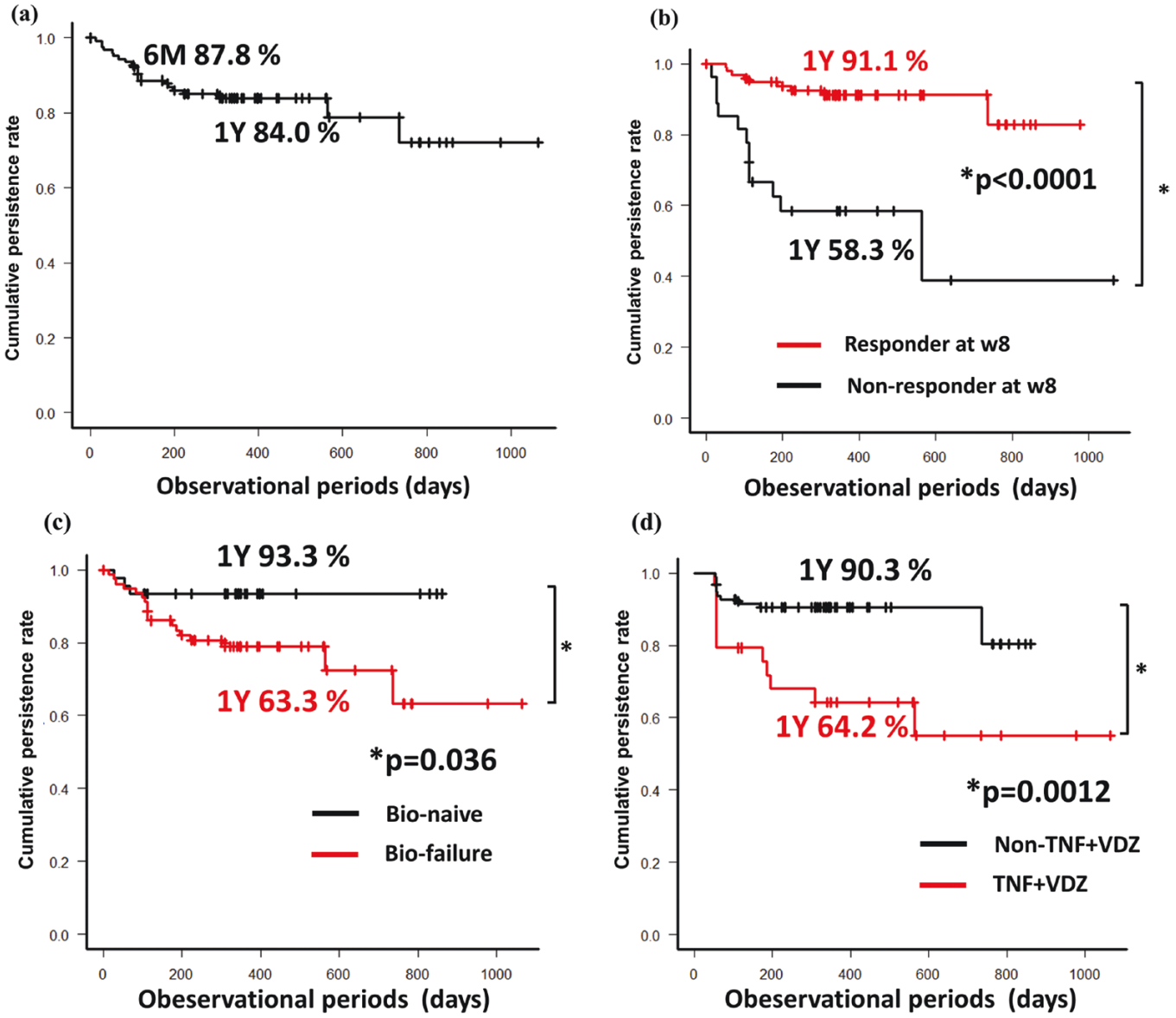

Figure 4. Cumulative persistence rate of UST (A) in the overall population, (B) classification with the presence of clinical response at week 8, (C) classification with previous exposure to biologics (bio-naïve and bio-failure), and (D) classification with previous exposure to both anti-TNF and VDZ.

Table 4. Predictive factors associated with 1-year UST persistence in univariate analysis.

	Univariate analysis	
	Cumulative persistence rate (%)	*P*-value
CRP (mg/dL)		
< 0.28	81.7%	.327
≥ 0.28	86.3%	
Extent of the disease		
E1–2	94.0%	.186
E3	82.3%	
Clinical course		
Chronic continuous type	74.6%	.234
Relapse-remitting type	86.8%	
PSL-dependent		
Absence	90.9%	.381
Presence	81.3%	
PSL-resistant		
Absence	82.6%	.494
Presence	100%	
Concomitant prednisolone		
Absence	83.4%	.561
Presence	85.0%	
Concomitant IM		
Absence	82.3%	.453
Presence	86.7%	
Bio primary nonresponder		
Absence	86.6%	.092
Presence	74.0%	
Bio secondary nonresponder		
Absence	84.9%	.647
Presence	82.8%	
Anti-TNF alone		
Absence	79.9%	.126
Presence	92.5%	
VDZ alone		
Absence	85.5%	.061
Presence	62.5%	
Anti-TNF + VDZ		
Absence	90.3%	.0012
Presence	64.2%	
TOF		
Absence	84.0%	.822
Presence	84.4%	
Previous use of bio/JAKis		
Absence (Bio-naïve)	93.3%	.0385
Presence (Bio-exposure)	63.3%	
Response at week 8		
Nonresponse at week 8	91.1%	<.001
(response to UST with or without additional therapy)	58.3%	
Response at week 8		
Nonresponse at week 8	91.6%	<.001
(response to UST alone)	66.7%	

for patients with bio-naïve UC were suggested to be 12.7%–66.7% and 7.2%–40.6%, respectively.[21]

This study included 36% bio-naïve patients and showed that the remission and response rates were over 70% and 80%, respectively, at week 56 in the bio-naïve group. This is the first real-world data demonstrating the high effectiveness of UST for the treatment of patients with bio-naïve UC. In UC with bio-failure, at 56 weeks following UST induction, the remission and response rates were 42%–54% and 65%–75% in this cohort; additionally, the effectiveness was influenced by the number of biologics and previous TOF exposure. In the UNIFI trial,[10] the significant superior efficacy of UST compared with placebo was demonstrated in both bio-naïve and bio-exposure, whereas the group with bio-naïve had higher remission and response rates than the bio-exposure group, which was consistent with the results of clinical trials regarding JAKis[4] and novel monoclonal antibodies, including anti-IL-23 antibody.[22] According to the UNIFI long-term extension trial,[23] the symptomatic remission rate at 8 and 52 weeks following UST induction was 75.8% and 71.6% in the group with bio-naïve and 62.9% and 48.6% in the group with bio-failure, respectively, which was suggested to be equivalent to the results of our retrospective cohort. The previous studies regarding the effectiveness of UST in clinical practice are summarized in Table 6.[11–15,24–26] Our results of the remission rate in the induction and maintenance phases were higher than those of other studies conducted in western countries, which was associated with the inclusion of 36% bio-naïve patients in this cohort. Moreover, this study represented that remission and response rates in bio-failure group as well as bio-naïve group tended to increase during the follow-up period, which possibly contributed to a delayed response to UST after 16 weeks.

Our multivariate analysis showed that previous use of both anti-TNF and VDZ and chronic continuous UC were negative predictive factors for the response to UST at week 8. In our study, although high UST effectiveness was shown regardless of the number of previously exposed agents, bio-failure with previous anti-TNF and VDZ exposure was lower than that with other agents. Two previous studies by Amiot A et al. and Honap et al.[12,15] on UST therapy for inducing UC remission have demonstrated that previous exposure to both anti-TNF and VDZ was a predictive factor for nonremission, which is consistent with our results. A previous study with in vitro and human mucosal specimens demonstrated that IL-23 upregulation was involved with anti-TNF or VDZ-resistant pathophysiology in IBD,[27–29] suggesting that blocking the IL-12/23 pathway was reasonable for patients with UC with anti-TNF or VDZ failure. In our cohort, patients with UC with previous exposure to anti-TNF or VDZ, but not both, frequently achieved clinical remission and response rates compared with those with previous exposure to both anti-TNF and VDZ. Previous studies have reported that patients with UC who were nonresponders to VDZ following failure to respond to anti-TNF antibody had higher levels of serum IL-6[30] and mucosal infiltration of eosinophils[31] than those who were responders to VDZ following failure to respond to anti-TNF antibody. Previous studies have indicated that eosinophilia led to the release of Th2-related cytokines, including IL-5 and IL-13, which are suggested to be associated with disease severity and complicated UC course.[31] Therefore, the IL-6 pathway and eosinophilia might play a key role in resistance to UST in previous exposure to both anti-TNF and

Table 5. Predictive factors associated with 1-year persistence of UST in multivariate analysis.

	Univariate analysis		Multivariate analysis	
	Cumulative persistence rate (%)	*P*-value	HR (95% CI)	*P*-value
Previous use of bio/JAKis	93.3	.0385*	2.30 (0.59–8.94)	.228
Absence (Bio-naïve)	63.3			
Presence (Bio-exposure)				
Previous use of anti-TNF and VDZ	90.3	.00115*	1.68 (0.54–5.21)	.372
Absence	64.2			
Presence				
Response at week 8	91.1	<.001	8.19 (1.06–63.45)	.0439
Nonresponse at week 8	58.3			
(response to UST with or without additional therapy)				
Response at week 8	91.6	<.001	1.98 (0.22–17.78)	.541
Nonresponse at week 8	66.7			
(response to UST alone)				

Table 6. Previously reported real-world data regarding UST for UC.

	N	Bio-failure (%)	Concomitant systemic steroid (%)	Remission rate		Steroid-free remission rate		Persistence rate (1 year)	Adverse event (%)
				Induction (12–16 weeks)	Maintenance (52 weeks)	Induction (12–16 weeks)	Maintenance (52 weeks)		
Ochsenkuhn T et al.[1]	19	95%	47.4%	58%	53%	10%	10%	73.6%	36.8%
Amiot A and Fumery M.[2][3]	103	99%	39.8%	40%	34%	35%	30%	58.4%	7.8%
Chaparro M et al.[4]	95	100%	56%	35%	33%	—	32%	63%	3.1%
Chiappetta MF, et al.[5]	68	97%	—	—	—	31%	50%	87%	1.5%
Thunberg J, et al.[6]	133	98%	25%	17%	32%	22%	48%	66%*	—
Hong SJ, et al.[7]	66	92%	35%	43%	45%	32%	35%	65%	12.1%
Honap S et al.[8]	110	96%	59%	46.9%	—	37%	—	76.4%	18%
Phoenix cohort	150 (125)	64%	33.6%	55.4%	63.4%	48%	59%	84.0%	6.4%

VDZ. However, in these studies, blood and colonic samples were collected before VDZ induction; therefore, whether higher IL-6 levels and mucosal eosinophilia were continuously observed following VDZ administration in patients with UC with previous anti-TNF exposure remains unknown. Elucidating the pathophysiology and verifying the therapeutic strategy including novel anti-IL-23 antibodies, JAKis, and other mode-of-action agents for UC with these predictive factors of nonresponse to UST including previous anti-TNF and VDZ exposure and chronic continuous type are necessary. In this study, laboratory data including Alb, CRP, LRG, and fecal calprotectin levels were not fully satisfied as predictive biomarkers for clinical effectiveness. To optimize the therapy for refractory UC, future investigations regarding predictive biomarkers for the effectiveness of UST must be performed.

In our cohort, the 1-year persistency of UST was as high as 84%. A recent review has shown that Th1 and Th17 activated by IL-12 and -23 play a major role in sustained chronic inflammation in any phase of UC,[20] thereby contributing to the high rate of maintaining remission. Therefore, considering the perspective of the mode of action of UST that blocks IL-12 and -23, the good efficacy and persistency of UST were theoretically reasonable.

Notably, the 1-year persistency in bio-naïve UC was remarkably high at 93.4% in this study. In UC with bio-failure, the persistency of the group with previous exposure to anti-TNF or VDZ alone was 87.6%, whereas 64.2% of those with previous exposure to both anti-TNF and VDZ were significantly lower than those with the abovementioned 2 groups. From the perspective of response to UST at week 8 including additional therapy with UST, persistency with responders at week 8, regardless of additional therapy, was significantly higher (91.1%) than that with nonresponders at week 8, regardless of additional therapy (58.3%). Multivariate analysis revealed that response at week 8, regardless of additional therapy, was the only predictive factor for 1-year UST persistency. Based on the results, additional therapy, including CS (systemic and topical formation), GMA, and Tac, should be considered when we encounter patients with UC who will not achieve clinical response and remission with UST alone, particularly in cases with previous anti-TNF and VDZ exposure, which might contribute to improving clinical course and persistency. As UST has a safety profile with a lower risk

of severe infection, additional immunosuppressive therapy in combination with UST is likely to be applied compared with anti-TNF therapy. A previous study has demonstrated that tacrolimus along with UST was effective for severe UC.[32]

This study had several limitations. First, this was a retrospective cohort study. However, the Phoenix cohort comprised 7 referral IBD hospitals and had a large number of patients with UC in 1 region, reflecting real-world data regarding the effectiveness of UST on patients with bio-naïve and refractory UC. Second, the criteria of judgment for UST discontinuation and additional therapy to UST were not established and were assigned to each physician. Third, one-third of the population in this study did not reach the 1-year observational period. Therefore, the 1-year cumulative persistence rate may be estimated to be high. Additionally, in this retrospective study, only one-third of the patients underwent endoscopic evaluation before and after UST induction while over 75% of the patients underwent endoscopy before UST induction. Moreover, the interval of endoscopic evaluation after UST induction varied in each patient. The data regarding endoscopic responsiveness was regarded as paucity of reliability due to missing data and disunited timing of endoscopic evaluation. To elucidate the persistence of UST and achievement of endoscopic remission in long-term observational periods of over 1 year, further investigations in our cohort are required.

In conclusion, our study from the real-world Phoenix cohort demonstrated the promising effectiveness and persistency of UST therapy for UC with good safety profiles. Previous exposure to both anti-TNF and VDZ and the chronic continuous type were predictive factors for nonresponse at the induction phase. Additionally, clinical response at week 8 contributed to UST persistence. These predictive factors suggested that the clinical course and previous history of therapies before UST induction influenced not only the clinical response but also UST persistence. Our findings contribute to the establishment of an appropriate therapeutic strategy with UST for refractory UC.

Supplementary Material

Supplementary data are available at *Crohn's & Colitis 360* online.

Author Contributions

K.A., M.F., and H.N. provided major input into the conceptual development of the studies, analyzed the collected data, wrote the manuscript, and supervised all investigations. K.A., N.U., T.I., A.M., M.N., H.T., K.S., T.K., F.O., T.A., S.M., T.K., Y.Y., and D.H. managed and treated the enrolled patients and collected the data. M.F. and H.N. helped design the studies, interpret the data, and prepare/review the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interest

K.A. received lecture fees from Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, AbbVie GK., Pfizer Inc., JIMRO Co. Ltd., EA Pharma Co. Ltd., Mochida Pharmaceutical Co. Ltd. M.F. has received honoraria and had expenses paid to attend or give a presentation or advice at a meeting for EA Pharma Co., Ltd., AYUMI Pharmaceutical Corporation, AbbVie GK, Otsuka Pharmaceutical Factory, Inc., Zeria Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Nippon Kayaku Co., Ltd., elpharma Co., Ltd., Pfizer Japan Inc., Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Olympus Corporation, Celltrionhealthcare.jp, Alfresa Pharma Corporation, Mylan Inc., Boston Scientific Corporation, Covidien Japan, Inc., FUJIFILM Corporation, Fuji Chemical Industries Co., Ltd., JIMRO Co., Ltd. and received research grants from EA Pharma Co., Ltd., AYUMI Pharmaceutical Corporation, AbbVie GK, Otsuka Pharmaceutical Factory, Inc., Zeria Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Nobelpharma Co., Ltd., Pfizer Inc., Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., JIMRO Co., Ltd., Kamui Pharma. Inc. N. U. has received grant from Pfizer Inc. T.I. received lecture fees from Janssen Pharmaceutical Co., Ltd. and Grants for commissioned/joint research from Gilead Sciences, Inc., Janssen Pharmaceutical K.K., Eli lilly Co., Ltd., Takeda Pharmaceutical Co. Limited, Pfizer Japan, Inc. M.N. received lecture fees from AbbVie GK, Eisai Co., Ltd., EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd. H.T. received lecture fees from JIMRO Co., Ltd., AbbVie GK, EA Pharma Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K., Nikkiso Co., Ltd., Nippon Kayaku Co., Ltd. and Takeda Pharmaceutical; and has received research grants from AbbVie GK, Janssen Pharmaceutical K.K., EA Pharma, Takeda Pharmaceutical, AstraZeneca K.K, and Kissei Pharmaceutical Co., Ltd. T.K. is a member of endowed chair by Miyarisan Pharmaceutical CO., Ltd., JIMRO Co., Ltd., Mochida Pharmaceutical Co., Ltd., and Kyorin Pharmaceutical CO., Ltd. H.N. reports receiving personal fees from Abbvie Inc., Takeda Pharmaceutical CO.,Ltd., Mitsubishi Tanabe Pharm Corperation, Janssen Pharmaceutical K.K, Gilead Sciences Inc., Pfizer Inc., EA Pharma CO.,Ltd., Kyorin Pharmaceutical CO.,Ltd., Mochida Pharmaceutical CO.,Ltd., VIATRIS Inc, JIMRO Co., Ltd., and Daiichi Sankyo Co., Ltd, scholarship grants from Nippon Kayaku Co.,Ltd., Mochida Pharmaceutical CO.,Ltd., Kyorin Pharmaceutical CO.,Ltd., Zeria Pharmaceutical CO.,Ltd., Mitsubishi Tanabe Pharma Corperation, and EA Pharma CO.,Ltd., research grants from Hoya Group Pentax Medical, Abbvie Inc., and endowed chair from Miyarisan Pharmaceutical CO.,LTD.,JIMRO Co.,Ltd., Mochida Pharmaceutical Co.,Ltd., and Kyorin Pharmaceutical CO.,Ltd.

Data Availability

The data underlying this article will be shared on reasonable request by the corresponding author.

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