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Real-World Data on Short-Term and Long-Term Treatment Results of Ustekinumab in Patients with Steroid-Resistant/Dependent Ulcerative Colitis

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Keywords
Ustekinumab · Ulcerative colitis · Real-world data · Biologic agents · Prednisolone

Abstract
Introduction: Ustekinumab is an IgG1 kappa monoclonal antibody directed against the common p40 subunit of interleukin-12 and interleukin-23, which activate Th1- and Th17-mediated immune responses, respectively. It has proven efficacy for the treatment of moderate to severe ulcerative colitis (UC) in the UNIFI phase III clinical trial; however, data on its efficacy in the real world are limited. In this study, we aimed to assess the real-world efficacy of ustekinumab. ***Methods:*** This observational study included 30 patients with UC who received ustekinumab from April 2020 to April 2022. We examined demographic information, disease type and activity (Mayo score, partial Mayo score [PMS]), use of biologics, concomitant use of predonisolone (PSL), 8-week ustekinumab clinical response rate, remission induction rate, 44- and 152-week remission maintenance rate, continuation rate, and 44-week steroid-free remission rate. The primary outcomes were the short- and long-term efficacy of ustekinumab. ***Results:*** Included patients (53% women; mean age: 41.2 years [16–80 years]) had an average disease duration of 86 weeks. The Mayo score (median) was 7.4 and the PMS was 5.4. Two (7%), 24 (80%), and four (13%) patients had a Mayo endoscopic subscore (MES) of MES1, MES2, and MES3, respectively. The median serum CRP was 1.0 mg/dL. Five patients had no history of biotherapy (naive), while eight and 17 had a history of one and two or more biologic agents, respectively. Eight patients were PSL-resistant and 22 were PSL-dependent. The 8-week clinical response rate was 73% and the clinical remission induction rate was 70%. The remission maintenance rates at 44 and 152 weeks were 67% and 63%, respectively. The ustekinumab retention rate was 67% (86-week mean follow-up period). Regarding biologic failure cases, the clinical response rate in the failure group with up to one biologic agent (including naive cases) was 84.6%, which was higher than the 58.0% rate in the failure group with two or more biologic agents ($p = 0.06$). Steroid-free remission rates at 44 and 152 weeks were 63% each. In the logistic regression analysis parameters for discontinuation of ustekinumab, only PMS remained significant after multivariate analysis ($p = 0.018$). ***Conclusion:*** Our

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study showed short-term and long-term ustekinumab effectiveness, especially with comparative low disease activity.

Introduction

Recently, the efficacy of biological therapy for ulcerative colitis (UC) has been remarkable, and its importance as a therapeutic method is increasing. Ustekinumab is an IgG1 kappa monoclonal antibody directed against the common p40 subunit of interleukin-12 and interleukin-23, which activate Th1- and Th17-mediated immune responses, respectively. Ustekinumab had proven efficacy for the treatment of moderate to severe UC in the UNIFI phase III clinical trial [1]. However, the efficacy of ustekinumab in real-world data is limited [2–8]. Ustekinumab became available for use in Japan in March 2020 as it was covered by health insurance. We verified the short-term and long-term efficacy and safety of ustekinumab in patients with steroid-dependent/resistant so-called refractory UC who were administered ustekinumab at our hospital.

Materials and Methods

This observational study included 30 patients diagnosed with UC who received ustekinumab from April 2020 to April 2022 at our hospital. Patients were enrolled every 8–12 weeks and followed up on an outpatient basis at the internal medicine booth. The primary outcomes were the short- and long-term efficacies of ustekinumab. Data were retrospectively analyzed as follows: patient demographics (age, sex, duration of disease), UC disease type, disease activity (using Mayo score and partial Mayo score [PMS]), use of biologics, concomitant use of predonisolone (PSL), 8-week clinical response rate for ustekinumab, remission induction rate, and 44- and 152-week remission maintenance, continuation, and bio-failure rates. We also examined the clinical response rate for patients and the steroid-free remission rate at 44 weeks. Data regarding patient characteristics, meditations, disease activity, and examination results were analyzed retrospectively by reviewing the patients' medical records. Steroid resistance was defined as no clear improvement within 1–2 weeks, despite appropriate treatment with steroids. Steroid dependence refers to a situation when the PSL dose is reduced, leading to exacerbation or relapse and a difficult withdrawal.

The exclusion criteria included age <18 years, diagnosis of Crohn's disease or IBD-unclassified (IBDU), and a history of surgery. All patients were prescribed ustekinumab per product license, which was administered intravenously at a dose of 6 mg/kg at baseline, followed by 90 mg subcutaneously at weeks 8 then 8–12 according to clinical evaluation.

The clinical response rate was defined as a Mayo score of 30% or more from baseline, accompanied by a decrease of 3 points or more and a 1-point Mayo rectal bleeding subscore (considered a decrease of 0 or 1 or greater or reaching 0 or 1). The clinical remission rate was defined as a Mayo score of less than or equal to 2 and none of the subscores being greater than 1.

The assessment of ustekinumab treatment was at 8 weeks for the short-term and at 44 and 152 weeks for the long-term treatment. All cases were evaluated at 44 weeks. Serious adverse reactions included anaphylaxis, serious infections, tuberculosis, and interstitial pneumonia. Other nonserious side effects, including headache, gastrointestinal disturbances (such as nausea and vomiting), dizziness, fatigue, arthralgia, and dermatitis, were not observed in this cohort.

Statistical analysis was performed by logistic regression analysis using SSPS (version 26.0, IBM Corp., Armonk, NY, USA). Categorical variables were summarized using absolute frequencies and percentages. Descriptive data were represented as means and standard deviation (SD) of the range or median for all continuous variables, with a significance level of 5%. In univariate analysis, only variables with $p < 0.05$ were selected for multivariate analysis using the variable reduction method. To assess the durability of treatment, a Kaplan-Meier survival analysis was performed, considering the time from the start of treatment to the last follow-up, treatment discontinuation, or loss of follow-up effect.

This retrospective study was conducted in accordance with the Declaration of Helsinki revised in 2002 and the Guidelines for Medical Research Involving Human Subjects (Japanese Ministry of Health, Labor, and Welfare). The study was approved by the Ethics Committee of Kindai University Hospital [approval no. 29-023]. The need for informed consent was waived by the Ethics Committee of Kindai University Hospital. Data were collected anonymously. Information about patient characteristics, meditations, disease activity, and examination results was analyzed retrospectively by reviewing their medical records.

Results

This study included 30 patients (53% women; mean age = 41.2 [16–80] years), with an average disease duration of 86 weeks. Twenty-four cases were of the extensive colitis type and six were of the left-sided colitis type. The Mayo score (median) was 7.4 and the PMS score was 5.4. Regarding the Mayo endoscopic subscore (MES), two (7%), 24 (80%), and four (13%) patients had MES1, 2, and 3, respectively. The median serum CRP was 1.0 mg/dL. Five patients had no history of biotherapy (naive), while eight and 17 had a history of one and two or more biologic agents, respectively. Biotherapy for the eight patients with a history of one drug included infliximab for four patients, tofacitinib for two, and vedolizumab for two. Biotherapy for the 17 patients with a history of two biologic agents included anti-TNF + tofacitinib for 10, anti-TNF + anti-TNF for two, anti-TNF + tacrolimus for two, anti-TNF + vedolizumab for two, and

Table 1. Baseline characteristics of ustekinumab-treated patients with UC

Variable	
Sex, male, *n* (%)	14 (46)
Age at start of ustekinumab, years, median (IQR)	41.2 (26–56.5)
Disease duration, years, median (IQR)	8.7 (4–12.5)
Disease extent, *n* (%)	Extensive colitis 24 (80) Left-sided colitis 6 (20)
PMS, median (IQR)	5.4 (4.25–6.00)
MES 3, *n* (%)	4 (13)
MES 2, *n* (%)	24 (80)
MES 1, *n* (%)	2 (7)
Serum CRP, mg/dL, median (IQR)	1.0 (0–1.05)
Previous prior biological treatment	
Bio naïve	5
Bio 1 agent	8
Anti-TNF	4
Tofacitinib	2
Vedolizumab	2
Bio ≥2 agent	17
Anti-TNF + tofacitinib	10
Anti-TNF + anti-TNF	2
Anti-TNF + tacrolimus	2
Anti-TNF + vedolizumab	1
Anti-TNF + tofacitinib + vedolizumab	2
PSL resistance, *n* (%)	8 (27)
PSL dependence, *n* (%)	22 (73)
AZA combination, *n* (%)	12 (40)

PMS, partial Mayo score; MES, Mayo endoscopic subscore; TNF, tumor necrosis factor; CRP, C-reactive protein; PSL, prednisolone; AZA, azathioprine.

anti-TNF + tofacitinib + vedolizumab for two patients. Eight patients were PSL-resistant and 22 were PSL-dependent. The rate of azathioprine (AZA) usage was 40% (12/30) (Table 1). Ustekinumab treatment was initiated every 12 weeks in all patients. Of them, 15, who had an inadequate response, were subsequently treated every 8 weeks.

The clinical response rate at 8 weeks was 73% and the induction of clinical remission was 70% (Table 2). The maintenance rates of remission at 44 (1 year) and 152 (3 years) weeks were 67% and 63%, respectively (Table 2). The ustekinumab persistence rate was 67% (mean follow-up period of 86 weeks) (Fig. 1).

Regarding biologic failure cases, the clinical response rate in the failure group with up to one biologic agent (including bio-naive cases) was 84.6%, which was higher than the rate of 58.0% in the failure group with two or more biologic agents ($p = 0.06$) (Fig. 2). In the group with no effect of ustekinumab, ≥2 biologic agents were administered in all cases ($p = 0.065$); the median Mayo score was 9.7, which was higher than that for the group with the ustekinumab effect (median Mayo score of 6.7).

Steroid-free remission rates at 44 and 152 weeks were 63% and 63%, respectively (Table 2). No relationship was observed between efficacy and steroid resistance or dependency. Regarding safety, no serious adverse events were observed in either group. For logistic regression parameters for discontinuation of ustekinumab, univariate analysis showed significant differences in PMS, MES, bloody stool, and physician's global assessment (PGA) score. In multivariate analysis, only the PMS showed a significant difference ($p = 0.018$, OR = 0.411, 95% CI: 0.197–0.858). In this study, we found that ustekinumab tended to be more effective in groups with relatively mild disease (Table 3). There were no serious adverse reactions including nonserious side effects in this cohort.

Discussion

This study investigated the efficacy and safety of short-term (8 weeks) and long-term (44 and 152 weeks) real-world data on ustekinumab usage for steroid-dependent/

Table 2. Clinical response, clinical remission, and steroid-free remission rate in patients with UC at weeks 8, 44, and 156

Period	Clinical response, %	Clinical remission, %	Steroid-free remission, %
8 weeks	73	70	70
44 weeks	73	67	63
152 weeks	73	63	63

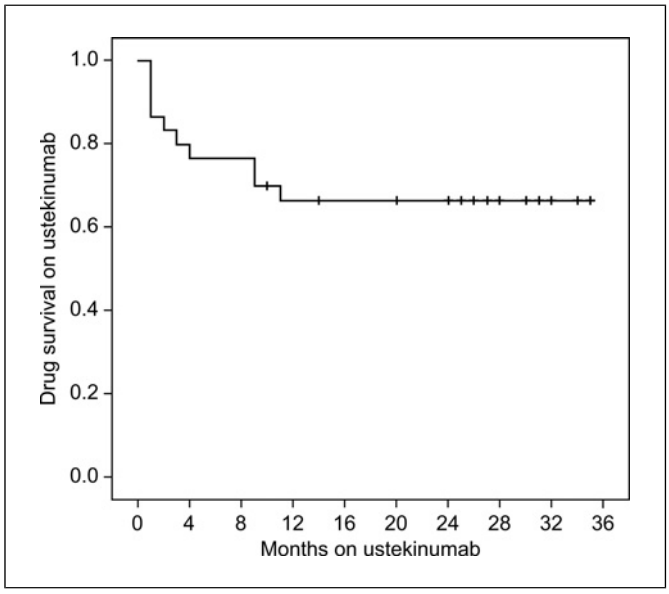

Fig. 1. Kaplan-Meier curve illustrating ustekinumab persistence.

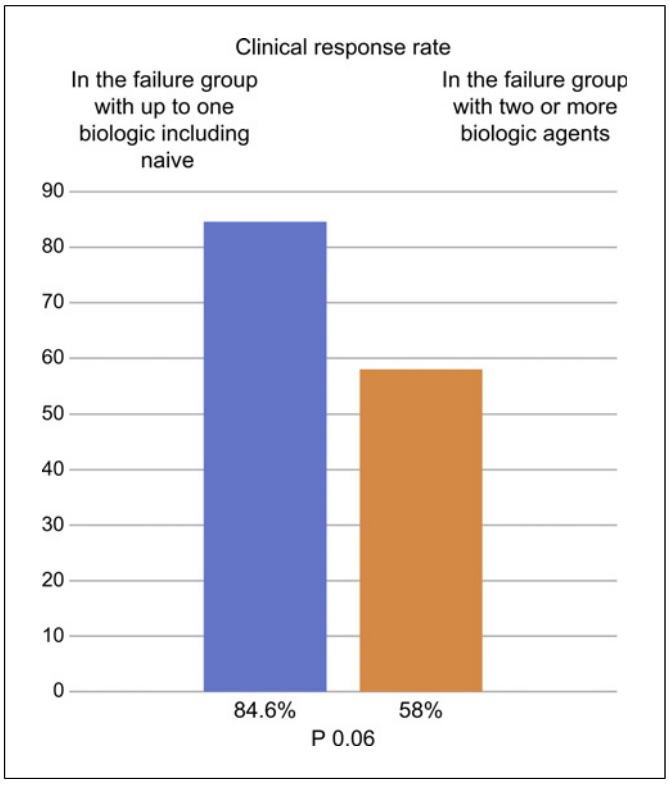

Fig. 2. Clinical response rate in the failure group with up to one biologic (including naïve) and in two or more biologic agent failure groups.

resistant refractory UC in a Japanese institution. In this cohort, 83.3% (25/30) of the patients used TNF-α antibodies as prior treatment. We provided real-world data showing a 73% 8-week clinical response rate and a remission induction 70%. The remission maintenance rates at 44 and 152 weeks were 67% and 63%, respectively. Steroid-free remission rates at 44 and 152 weeks were 63% and 63%, respectively. The overall persistence rate was 67%, and the average follow-up period was 86 weeks (20 months).

The GETAID trial conducted a retrospective study of the efficacy and safety of ustekinumab in patients with moderate to severe active UC with a PMS of 6. The clinical remission rate was 40% at 12–16 weeks and the clinical remission rate without steroids was 35%. We found higher rates in our study. This may be attributed to relatively mild patient-based disease activity, with a PMS of 5.5 compared with a PMS of 6 in the GETAID trial [2].

The Swedish IBD Registry (SWIBREG) reported short- and long-term outcomes of UC patients treated with ustekinumab [8]. In that study, which included 133 patients, the primary outcome of ustekinumab persistence at 16 weeks was 86% and 67% after a median follow-up of 32 weeks. Although these were higher than our results, only three patients in this study received no biologics and no tofacitinib. The persistence rate reported was lower than that reported in the UNIFI study, which included only patients who responded to induction therapy [1]. Data from the ENEIDA registry showed a 63% persistence rate at 56 weeks [3], which was the same as our 44-week persistence rate. In our study, the group that continued at 44 weeks was able to continue at 152 weeks.

Recent studies on steroid-free clinical remission data showed similar rates between 30% and 40% [2, 4, 6, 7]. Our 44-week rate of 63% was higher than these previous rates and comparable with the results of Dalal et al. [5], who reported a rate of 55% after dose escalation, which may be due to the effect of an increased dose by the physician.

Table 3. Cox regression parameters for discontinuation of ustekinumab

Factor	Univariate analysis				Multivariate analysis			
	p value	OR	95% CI		*p* value	OR	95% CI	
Age	0.585	1.012	0.969	1.058				
Duration of disease	0.611	1.034	0.909	1.176				
PMS	0.018	0.411	0.197	0.858	0.018	0.411	0.197	0.858
Alb	0.092	2.993	0.837	10.705				
CRP	0.146	0.668	0.387	1.151				
Hb	0.542	1.139	0.749	1.733				
Sex								
Male	Reference	1.000						
Female	0.140	3.571	0.659	19.341				
UC disease type								
Pancolitis	Reference	1.000						
Left-sided	0.542	2.059	0.202	20.959				
MES								
MES 1 and 2	Reference	1.000			Exclusion	–		
MES 3	0.044	0.079	0.007	0.933	–	–	–	–
PSL resistance								
No	Reference	1.000						
Yes	0.423	0.490	0.086	2.805				
Previous biotherapy								
<2	Reference	1.000						
≥2	0.065	0.119	0.012	1.138				
Defecation								
Mild/moderate	Reference	1.000						
Severe	0.546	0.600	0.114	3.148				
Bloody stool								
Mild/moderate	Reference	1.000			Exclusion	–		
Severe	0.044	0.079	0.007	0.933	–	–	–	–
PGA								
Mild/moderate	Reference	1.000			Exclusion	–		
Severe	0.014	0.048	0.004	0.545	–	–	–	–

Alb, albumin; CRP, C-reactive protein; MES, Mayo endoscopic subscore; PGA, physician's global assessment; Hb, hemoglobin; PMS, partial Mayo score; PSL, prednisolone; UC, ulcerative colitis.

In the logistic regression parameters for discontinuation of ustekinumab, univariate analysis showed significant differences in PMS, MES, bloody stool, and PGA, with significant results in multivariate analysis in PMS only. In addition, in the analysis of prior treatment, the bio-naïve and one-drug ineffective groups tended to be more responsive than the group in which two or more drugs were ineffective, although no significant difference was observed ($p = 0.06$). Our results show that positive results can be expected when no more than one bio-ineffective agent was previously utilized.

In this cohort, no effect was observed in severe cases such as acute severe UC. Only limited evidence of treatment for acute severe UC exists in previous reports [9].

In terms of safety regarding side effects, no serious adverse events were observed in the effective or noneffective groups. From these results, ustekinumab administration in the failure group with up to one biologic agent (including naive cases) was appropriate for the treatment of mild to moderate steroid-resistant/dependent UC. The concomitant rate of AZA treatment was low at 40%, and although we did not examine the use of concomitant AZA

in this study, Aoki et al. [10] reported that there was no significant difference between ustekinumab monotherapy and immunosuppressants plus concomitant treatment.

The limitations of this study include a small sample size and the retrospective single-institution design. The dosing interval of ustekinumab in the maintenance phase was approximately 12 weeks on average, although it ranged from 8 to 12 weeks at the discretion of the attending physician.

In our study, ustekinumab was effective in the short- and long-term treatment in the refractory UC cohort in Japanese patients. However, many patients had relatively low disease activity at the time of ustekinumab introduction. Thus, the clinical response rate and remission induction rate were higher than those in previous reports. In addition, the single-drug failure group, including the bio-naïve group, tended to have a higher clinical response rate than did the two-or-more-bio-drug failure group.

Statement of Ethics

This retrospective study was conducted in accordance with the Declaration of Helsinki revised in 2002 and the Guidelines for Medical Research Involving Human Subjects (Japanese Ministry of Health, Labor, and Welfare). The study was approved by the Ethics Committee of Kindai University Hospital [approval no. 29-023]. The need for informed consent was waived by the Ethics Committee of Kindai University Hospital. Data were collected anonymously. Information about patient characteristics, meditations, disease activity, and examination results was analyzed retrospectively by reviewing their medical records.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yoriaki Komeda contributed to the study conception and wrote the first draft of the manuscript. George Tribonias and Masatoshi Kudo contributed to the review and critical revision of the manuscript. Yoriaki Komeda, Masashi Kono, Kohei Handa, Shunsuke Omoto, Mamoru Takenaka, Satoru Hagiwara, Naoshi Nishida, Naoko Tsuji, and Hiroshi Kashida managed the patients. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019 Sep;381(13):1201–14.
2 Amiot A, Filippi J, Abitbol V, Cadiot G, Laharie D, Serrero M, et al. Effectiveness and safety of ustekinumab induction therapy for 103 patients with ulcerative colitis: a GETAID multicentre real-world cohort study. Aliment Pharmacol Ther. 2020 Jun;51(11):1039–46.
3 Chaparro M, Garre A, Iborra M, Sierra-Ausín M, Barreiro-de Acosta M, Fernández-Clotet A, et al. Effectiveness and safety of ustekinumab in ulcerative colitis: real-world evidence from the ENEIDA registry. J Crohns Colitis. 2021 Nov;15(11):1846–51.
4 Chiappetta MF, Viola A, Mastronardi M, Turchini L, Carparelli S, Orlando A, et al. One-year effectiveness and safety of ustekinumab in ulcerative colitis: a multicenter real-world study from Italy. Expert Opin Biol Ther. 2021 Nov;21(11):1483–9.
5 Dalal RS, Esckilsen S, Barnes EL, Pruce JC, Marcus J, Allegretti JR. Predictors and outcomes of ustekinumab dose intensification in ulcerative colitis: a multicenter cohort study. Clin Gastroenterol Hepatol. 2022 Oct;20(10):2399–401.e4.
6 Fumery M, Filippi J, Abitbol V, Biron A, Laharie D, Serrero M, et al. Effectiveness and safety of ustekinumab maintenance therapy in 103 patients with ulcerative colitis: a GETAID cohort study. Aliment Pharmacol Ther. 2021 Oct;54(7):944–51.
7 Dhaliwal J, McKay HE, Deslandres C, Debruyn J, Wine E, Wu A, et al. One-year outcomes with ustekinumab therapy in infliximab-refractory paediatric ulcerative colitis: a multicentre prospective study. Aliment Pharmacol Ther. 2021 Jun;53(12):1300–8.
8 Thunberg J, Björkqvist O, Hedin CRH, Forss A, Söderman C, Bergemalm D, et al. Ustekinumab treatment in ulcerative colitis: real-world data from the Swedish inflammatory bowel disease quality register. United European Gastroenterol J. 2022 Sep;10(7):631–9.
9 Segal JP, Quraishi MN. Lack of evidence for the use of ustekinumab for acute severe ulcerative colitis. United European Gastroenterol J. 2021 Mar;9(2):279.
10 Aoki Y, Sujino T, Kawaguchi T, Sugimoto S, Shimada F, Yoshimatsu Y, et al. Effectiveness and durability of ustekinumab therapy with or without immunomodulators for ulcerative colitis patients in Japan. Crohns Colitis 360. 2022 Mar;4(2):otac010.