Inflammatory Bowel Diseases, 2023, **29**, 548–554
https://doi.org/10.1093/ibd/izac105
Advance access publication 7 June 2022
Original Research Articles - Clinical

Feasibility of a Clinical Decision Support Tool for Ustekinumab to Predict Clinical Remission and Relapse in Patients With Crohn's Disease: A Multicenter Observational Study

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Background: Ustekinumab was recently approved for the treatment of moderate to severe Crohn's disease (CD). Although the ustekinumab Clinical Decision Support Tool (UST-CDST) was able to predict ustekinumab responsiveness in a clinical trial, it is not clear whether UST-CDST can also predict a future clinical relapse following ustekinumab therapy in the real-life setting.

Methods: We enrolled patients with moderate to severe CD who were refractory to conventional therapies and who showed a clinical response after induction therapy with ustekinumab and monitored them until the relapse. We performed a Cox proportional hazard analysis to investigate the predictive capability of UST-CDST for a clinical disease relapse.

Results: Clinical remission rates at week 20 were 25.0% for low-probability responders, 66.7% for intermediate-probability responders, and 75.0% for high-probability responders. The high-probability responders were more likely to achieve clinical remission at week 20 compared with the low-probability responders. Among 99 patients with moderate to severe CD, 37 (37.4%) experienced a clinical relapse during the median follow-up period of 18.0 months of ustekinumab treatment. The cumulative relapse rates were 70.0% in the low-probability responders, 35.9% in the intermediate-probability responders, and 22.5% in the high-probability responders ($P = .001$). In a multivariable Cox proportional hazard analysis, the high-probability responders and intermediate-probability responders had a lower risk of clinical relapse than the low-probability responders. Receiver operating characteristic analysis using UST-CDST to predict relapse revealed an area under the curve of 0.698.

Conclusions: The UST-CDST can predict clinical relapse in patients with moderate to severe CD subjected to ustekinumab therapy.

Lay Summary

Clinical decision tools are useful in stratifying patients for optimal treatment. Here, we validate the capacity of Ustekinumab Clinical Decision Support Tool to predict clinical remission and relapse in Korean patients with moderate to severe Crohn's disease.

Key Words: Crohn's disease, relapse, UST-CDST, ustekinumab

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; VDZ-CDST, Vedolizumab Clinical Decision Support Tool; UST-CDST, Ustekinumab Clinical Decision Support Tool; CDAI, Crohn's Disease Activity Index; BMI, body mass index; SD, standard deviation; IQR, interquartile range; ROC, receiver operating characteristic; AUC, area under the curves

Introduction

Biologic agents for patients with moderate to severe Crohn's disease (CD) refractory to conventional therapies have been the focus for rapid development recently. Consequently, clinicians now have a wide choice of drugs with various mechanisms of action to be used in patients with CD, including infliximab, adalimumab, vedolizumab, and ustekinumab.[1] Ustekinumab, a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit of interlukin-12 and interleukin-23, is the most recently approved agent for CD treatment that was shown to be characterized by long-term efficacy and safety in the UNITI-1, UNITI-2, and IM-UNITI clinical trials.[2] To overcome the strict trial design that cannot perfectly reflect real-life clinical practice, an increasing number of studies have assessed the real-life effectiveness and safety of ustekinumab treatment in patients with active CD in Western countries.[3] Although Ito et al reported that the

Received for publication: January 18, 2022. Editorial Decision: May 2, 2022

clinical remission rates at weeks 8 and 52 in moderate to severe CD treated with ustekinumab ($n = 40$) were 27.0% and 32.4%, respectively, studies including Asian populations are still scarce.[4,5]

The investigation of clinical factors or biomarkers that can predict clinical outcomes facilitates the clinical decision-making process regarding the choice of proper biologic agent for individual patients with CD [6]. Previous studies have suggested that active smoking, stricturing behavior, and severe disease course are negatively associated with the clinical response to ustekinumab in patients with CD.[3] In addition to clinical factors, biomarkers such as serum C-reactive protein (CRP), albumin, tumor necrosis factor (TNF)-α, and ustekinumab trough levels were investigated regarding their capacity to predict clinical outcomes for the optimization of ustekinumab treatment in these patients.[3] However, no predictive serum biomarkers consistently associated with ustekinumab response in patients with CD have been identified to date.[7,8]

Dulai et al developed and validated a Vedolizumab Clinical Decision Support Tool (VDZ-CDST) to predict the clinical response at week 26 in patients with active CD treated with vedolizumab who were enrolled in the GEMINI 2 phase 3 trial and VICTORY trial.[9] Dulai et al expanded the VDZ-CDST to predict exposure-efficacy relationships at week 14 and surgery risk over 12 months in patients with active CD who were treated with vedolizumab across multiple clinical trial cohorts.[1]. Alric et al recently demonstrated that the VDZ-CDST predicted clinical remission, steroid-free clinical remission, and CD-related surgery at week 48 in patients with active CD who were treated with vedolizumab, but not in those treated with ustekinumab using real-life data.[1]. Similar to the VDZ-CDST approach, Dulai et al developed the Ustekinumab Clinical Decision Support Tool (UST-CDST) to predict clinical remission at week 16 in active patients with CD treated with ustekinumab who were enrolled in the UNITI trial.[1]. However, UST-CDST has not yet been demonstrated as a prognostic factor for clinical disease relapse in real-life clinical practice. Therefore, we aimed to investigate the capacity of UST-CDST to predict clinical relapse in Korean patients with moderate to severe CD treated with ustekinumab in real-life clinical practice.

Methods

Patients

Between February 2019 and September 2021, 130 patients with moderate to severe CD refractory to conventional therapies treated with ustekinumab were enrolled at the Severance Hospital, Yonsei University College of Medicine (Seoul, Korea), Gangnam Severance Hospital (Seoul, Korea), and Seoul National University Bundang Hospital (Seongnam, Korea). Refractory moderate to severe CD was defined as CD refractory to conventional therapies, CD with primary nonresponse or loss of response to anti-TNF-α agents or vedolizumab, and CD with a Crohn's Disease Activity Index (CDAI) score >220.[13] The exclusion criteria were as follows: (1) patients younger than 18 years of age, (2) patients who did not achieve clinical remission or response at weeks 16-20, (3) patients with a follow-up period shorter than 4 months, or (4) patients with incomplete medical records disabling UST-CDST calculations. The initial intravenous ustekinumab infusion dose was weight-based (260 mg, <55 kg; 390 mg, between 55 and 85 kg; 520 mg, >85 kg), and the first induction subcutaneous dose was administered at week 8 (90 mg) followed by an assessment of clinical response at weeks 16-20. Subsequent maintenance subcutaneous dosing of 90 mg was allowed every 8 or 12 weeks after week 20, according to the treating physician's decision on dose optimization. This study was approved by the Institutional Review Boards of Severance Hospital, Yonsei University, and Seoul National University Bundang Hospital (IRB No. 4-2021-1117, B-2111-719-106).

Ustekinumab Clinical Decision Support Tool

The UST-CDST was calculated using the following 5 variables: no prior anti-TNF-α exposure (+2 points); no prior bowel surgery (+2 points); no active fistulizing disease at baseline (+1 point); no current or prior smoking history (+1 point); baseline albumin level (≤2.5g/dL, −3 points; >2.5 to ≤3.2g/dL, −1 point; >3.2 to ≤3.9g/dL, 0 point; >3.9 to ≤4.3g/dL, +1 point; >4.3g/dL, +3 points).[12] Patients with a UST-CDST score of 1 point or lower were assigned to the low-probability responders group, those with ≥2 to 4 points to the intermediate-probability responders group, and those with ≥5 points to the high-probability responders group.[12]

Data Collection and Outcomes

We retrospectively examined and collected the following data from the electronic medical records of the patients: sex, age, body mass index (BMI), disease duration, smoking history, extraintestinal manifestations, CD localization, the course of CD, perianal lesions, previous CD-related abdominal surgery, previous use of immunomodulatory drugs, previous use of anti-TNF-α drugs, previous use of vedolizumab, corticosteroid use at the initiation of ustekinumab, use of a combination of immunomodulators, dose intensification, CDAI, serum CRP level, and serum albumin level.

The primary outcome of this study was clinical relapse, which was defined as a therapeutic failure (additional corticosteroid use, withdrawal of ustekinumab, need for a CD-related surgery, or CD-related hospitalization) developing after the initial clinical response during the ustekinumab maintenance therapy. Shortening of the dose interval was not considered a treatment failure. The secondary outcome of this study was clinical remission at week 20, defined as a CDAI score lower than 150.

Statistical Analysis

Means and standard deviations (SD) or medians and interquartile range (IQR) were calculated for continuous variables, and numbers and percentages were calculated for categorical variables. Either 1-way ANOVA or the Kruskal-Wallis test was used to compare continuous variables, and either the χ^2 test or Fisher exact test was used for categorical variables, as appropriate. Kaplan-Meier analysis (log-rank test) was carried out to compare the cumulative clinical relapse rates of patients with active CD who were treated with ustekinumab in the low-, intermediate-, and high-probability responder groups. Cox proportional hazards analysis was carried out to reveal the independent risk factors of cumulative clinical relapse in patients with active CD treated with ustekinumab, with adjustment for various confounding factors. For the receiver operating characteristic (ROC) curves, the area under the curve (AUC) was calculated. Logistic regression analysis was performed to investigate the independent risk factors of

clinical remission at week 20 in active disease patients treated with ustekinumab, with adjustment for various confounding factors. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Armonk, NY, USA). Statistical significance was set at $P < .05$.

Results

Patient Baseline Characteristics

Of the 130 patients with refractory moderate to severe CD who started ustekinumab therapy between February 2019 and September 2021, 17 patients (13.1%) who were treated for less than 4 months were excluded due to primary nonresponsiveness to ustekinumab or a follow-up loss. Another 14 patients (10.7%) were excluded due to the lack of baseline serum albumin levels data. The remaining 99 CD patients (76.2%) treated with ustekinumab who reached clinical response at weeks 16-20 were included in this study. Sixty-four patients (64.6%) were male, and the mean age at ustekinumab induction was 36.9 ± 11.8 years (median, 34.0 years; interquartile range [IQR], 28.0-45.0 years). The mean disease duration at ustekinumab induction was 10.7 ± 6.2 years (median, 11.0 years; IQR, 5.0-14.0 years). Eighty-five patients (85.9%) had ileocolonic CD, 49 (49.5%) had a penetrating disease, and 56 (56.6%) had perianal lesions. Fifty patients (50.5%) had a history of CD-related abdominal surgery, 58 (58.6%) experienced failure of anti-TNF-α therapy, and 25 (25.3%) failed to respond to vedolizumab. Sixty-eight patients (68.7%) received concomitant immunomodulatory therapy, and 12 patients (12.1%) received concomitant corticosteroids at ustekinumab induction.

Relapse Rate and Relapse Prediction

The mean duration of ustekinumab treatment was 18.1 ± 7.8 months (median, 18.0 months; IQR, 12.0–24.0 months). Among the 99 patients with CD who achieved a clinical response to ustekinumab, 37 (37.4%) experienced clinical relapse during the ustekinumab maintenance treatment. The mean time to clinical relapse from ustekinumab initiation was 13.9 ± 8.6 months (median, 12.0 months; IQR, 6.0-22.0 months). Nineteen patients (19.2%) needed additional corticosteroid use, 8 patients (8.1%) withdrew from ustekinumab therapy, 11 patients (11.1%) needed CD-related surgery, and 22 patients (22.2%) needed CD-related hospitalization. Cox proportional hazard analyses showed that the previous use of vedolizumab (hazard ratio [HR], 3.166; 95% confidence interval [CI], 1.211-8.276; $P = .019$) and concomitant corticosteroid use at ustekinumab induction (HR, 3.201; 95% CI, 1.319-7.765; $P = .010$) were independently associated with clinical relapse during ustekinumab treatment for moderate to severe CD (Supplementary Table 1).

We stratified the relapse analysis by subtypes of relapse (CD-related complication and hospitalization) to provide essential prediction of disease progression. The cumulative relapse rates were 65.0% in the low-probability responders (UST-CDST ≤1), 30.8% in the intermediate-probability responders (UST-CDST ≥2 and ≤4), and 15.0% in the high-probability responders (UST-CDST ≥5; $P < .001$; Supplementary Table 2). In a multivariable Cox proportional hazard analysis, the high-probability responders had a lower risk of clinical relapse than the low-probability responders (HR, 0.233; 95% CI, 0.076-0.713; $P = .011$; Supplementary Table 2).

Prediction of Relapse Stratified According to UST-CDST

Twenty patients (20.2%) had a UST-CDST ≤1 (the low-probability responders group), 39 patients (39.4%) had a UST-CDST ≥2 and ≤4 (the intermediate-probability responders group), and 40 patients (40.0%) had a UST-CDST ≥5 (the high-probability responders group; Table 1). Body mass index, disease duration, disease location, disease course, previous CD-related abdominal surgery, previous anti-TNF-α use, previous vedolizumab use, previous opioid use, corticosteroid use at initiation, and serum CRP levels were significantly different between the 3 groups (Table 1).

Kaplan-Meier analysis (log-rank test) was carried out to compare the cumulative clinical relapse rates among the low-, intermediate-, and high-probability responders. The clinical relapse rates were 70.0% of low-probability responders, 35.9% of intermediate-probability responders, and 22.5% of high-probability responders, respectively ($P = .001$, χ^2 test). The UST-CDST differentiated the clinical relapse rate in patients with CD treated with ustekinumab ($P < .001$ log-rank test; Figure 1). Furthermore, the Cox proportional hazard analysis with various confounding factors showed that the high-probability responders group was characterized by a lower risk of clinical relapse than the low-probability responders group (HR, 0.389; 95% CI, 0.166-0.910; $P = .029$). The intermediate-probability responders group was also characterized by a lower risk of clinical relapse than the low-probability responders group (HR, 0.347; 95% CI, 0.136-0.884; $P = .027$; Table 2).

The ROC analysis using UST-CDST to predict the clinical relapse revealed an AUC of 0.698 (95% CI, 0.588–0.807; Figure 2).

Clinical Remission Rate at Week 20 and Prediction of Clinical Remission Stratified According to UST-CDST

The clinical remission rates at week 20 were 25.0% for low-probability responders, 66.7% for intermediate-probability responders, and 75.0% for high-probability responders ($P = .001$, χ^2 test, Table 3). We examined the CDAI subcomponent changes between baseline and week 20, stratified by the UST-CDST groups. The general well-being subcomponent score was significantly improved in the intermediate and high-probability responders group compared with low-probability responders group ($P = .002$, Supplementary Table 3 and Supplementary Figure 1). Subcomponent scores of abdominal pain (−35.0, −52.1, and −44.6 in low-, intermediate-, and high-probability responders, respectively; $P = .131$) and hematocrit level (1.9, −7.7 and −16.0 in low, intermediate- and high-probability responders, respectively; $P = .071$) were also differentially improved among the groups according to the UST-CDST, but this was not statistically significant (Supplementary Table 3 and Supplementary Figure 1). Furthermore, the logistic regression analysis including various confounding factors showed that the high-probability responders group was more likely to achieve clinical remission at week 20 compared with the low-probability responders group (odds ratio [OR], 4.437; 95% CI, 1.018-19.337; $P = .047$; Table 3). The intermediate-probability

Table 1. Baseline patient characteristics (N = 99).

Variables	Low Probability Responders (n = 20)	Intermediate Probability Responders (n = 39)	High Probability Responders (n = 40)	*P
Age (years)	37.8 ± 10.8	37.8 ± 10.5	35.7 ± 13.6	.682
Sex (male)	10 (50.0%)	13 (33.3%)	12 (30.0%)	.294
Body Mass Index (kg/m^2)	17.8 ± 2.6	20.8 ± 3.5	21.8 ± 3.0	<.001
Disease duration (years)	13.4 ± 6.3	11.3 ± 5.9	8.7 ± 5.9	.013
Smoking history	2 (10.0%)	3 (7.7%)	5 (12.5%)	.778
Extraintestinal manifestations	3 (15.0%)	4 (10.3%)	3 (7.5%)	.661
CD location				.003
Ileal	0 (0.0%)	2 (5.1%)	11 (27.5%)	
Colonic	1 (5.0%)	0 (0.0%)	0 (0.0%)	
Ileocolonic	19 (95.0%)	37 (94.9%)	29 (72.5%)	
CD behavior				<.001
Nonstricturing, nonpenetrating	2 (10.0%)	10 (25.6%)	20 (50.0%)	
Stricturing	0 (0.0%)	8 (20.5%)	10 (25.0%)	
Penetrating	18 (90.0%)	21 (53.8%)	10 (25.0%)	
Perianal lesion	10 (50.0%)	23 (59.0%)	23 (57.5%)	.796
Previous CD-related abdominal surgery	18 (90.0%)	24 (61.5%)	8 (20.0%)	<.001
Previous immunomodulator use	18 (90.0%)	38 (97.4%)	37 (92.5%)	.466
Previous anti-TNF alpha use	20 (100.0%)	32 (82.1%)	6 (15.0%)	<.001
Previous anti-TNF alpha number				<.001
0	0 (0.0%)	6 (15.4%)	34 (85.0%)	
1	9 (45.0%)	20 (51.3%)	6 (15.0%)	
2	11 (55.0%)	13 (33.3%)	0 (0.0%)	
Previous vedolizumab use	13 (65.0%)	11 (28.2%)	1 (2.5%)	<.001
Opioid use history	8 (40.0%)	5 (12.8%)	3 (7.5%)	.004
Concomitant medical history				
Corticosteroids at initiation	3 (15.0%)	8 (20.5%)	1 (2.5%)	.045
Immunomodulator at initiation	14 (70.0%)	26 (66.7%)	28 (70.0%)	.941
Dose intensification	16 (80.0%)	34 (87.2%)	29 (72.5%)	.267
Crohn's disease activity index	320.9 ± 95.3	307.6 ± 87.1	283.7 ± 64.2	.193
C-reactive protein (mg/L)	28.8 ± 28.0	11.9 ± 17.2	12.9 ± 21.4	.039
Albumin (g/L)	3.3 ± 0.5	3.8 ± 0.5	4.2 ± 0.4	.782

Variables are expressed as mean ± SD or n (%).
*P value for comparing low, intermediate, and high probability responder group.
Abbreviation: CD, Crohn's disease.

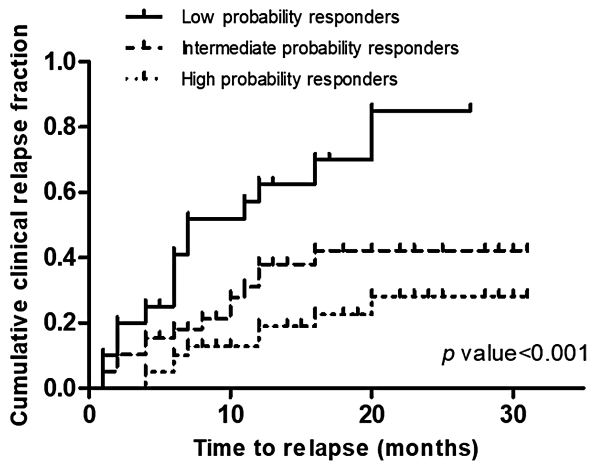

Figure 1. Cumulative clinical relapse fraction stratified according to the UST-CDST in patients with refractory moderate to severe CD treated with ustekinumab. Abbreviations: UST-CDST, Ustekinumab Clinical Decision Support Tool; CD, Crohn's disease.

responders group was more likely to achieve clinical remission at week 20 compared with the low-probability responders group, although the difference was not statistically significant (OR, 4.052; 95% CI, 0.961-17.078; P = .057; Table 3).

Discussion

One of the most important concepts of treatment optimization in the era of biologics is precision medicine based on clinical, laboratory, microbial, and genetic factors.[3,14-16] Dulai et al developed a UST-CDST scoring system that combined clinical and laboratory factors using a patient set from a phase 3 multicenter, double-blind, placebo-controlled randomized clinical trial (n = 781).[12] The UST-CDST includes prior anti-TNF-α exposure, prior bowel surgery, active fistulizing disease at baseline, current or prior smoking history, and baseline albumin levels. The authors assessed the capacity of UST-CDST to predict clinical remission rates at week 16 stratified by the probability of response (21.1% for low-probability responders, 34.2% for intermediate-probability responders, and 56.6% for

Table 2. Relapse rates and multivariable-adjusted hazard ratios of relapse according to CDST-UST (N = 99).

Variables	Low Probability Responders (*n* = 20)	Intermediate Probability Responders (*n* = 39)	High Probability Responders (*n* = 40)	*P* Trend
Relapse events				
Events	14 (70.0%)	14 (35.9%)	9 (22.5%)	0.001
Multivariable-adjusted HR (95% confidence interval)	(Reference)	0.389 (0.166-0.910)*	0.347 (0.136-0.884)*	

Variables are expressed as n (%).
Multivariable model adjusted for age, sex, body mass index, disease duration, extraintestinal manifestation, CD location, perianal lesion, previous immunomodulator use, opioid use history, corticosteroids at initiation, immunomodulator at initiation, dose intensification, CDAI, CRP
Abbreviations: HR, hazards ratio; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein
*P value <.05.

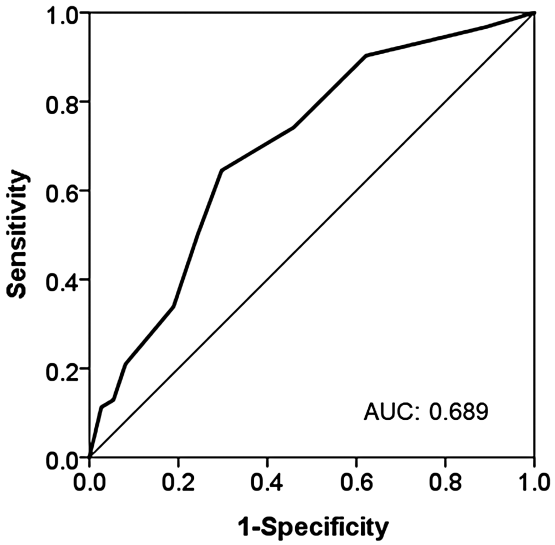

Figure 2. Receiver operating characteristic curves for UST-CDST to predict the clinical relapse. Abbreviation:UST-CDST, Ustekinumab Clinical Decision Support Tool.

high-probability responders, $P < .0001$)[12]. In our study, the clinical remission rates at week 20 were 25.0% for low-probability responders, 66.7% for intermediate-probability responders, and 75.0% for high-probability responders, and these values were similar to those reported by Dulai et al. However, an external validation is yet to be performed using a routine practice cohort as it is necessary to confirm the clinical utility of UST-CDST because of the heterogeneity of treatment effects across populations with CD. Moreover, not only prediction of remission induction but also prediction of disease relapse after induction therapy should be investigated.

Based on the data, we aimed to expand the utility of UST-CDST to predict clinical relapse in patients with moderate to severe CD treated with ustekinumab in a real-life setting. The relapse rate was as high as 70% in the low-probability responders group (UST-CDST ≤1), but it gradually decreased to 35.9% in the intermediate-probability responders group (UST-CDST ≥2 and ≤4) and to 22.5% in the high-probability responders group (UST-CDST ≥5; $P = .001$). Furthermore, the high-probability responders group was characterized by a significantly lower risk of clinical relapse than the low-probability responders group (HR, 0.389; 95% CI, 0.166-0.910; $P = .029$). The intermediate-probability responders group also had a lower risk of clinical relapse than low-probability responders (HR, 0.347; 95% CI, 0.136-0.884; $P = .027$) in the multivariable Cox proportional hazard analysis. Notably, these findings imply that UST-CDST can be useful in predicting not only the initial clinical response but also the treatment persistence of ustekinumab when selecting a biologic agent in an actual clinical practice. In previous studies, the AUC of VDZ-CDST for vedolizumab was 0.66 (95% CI, 0.57-0.76) in a clinical trial data set and 0.69 (95% CI, 0.57-0.82) in a real-life data set.[9,11] In the current study, the AUC of UST-CDST for ustekinumab was 0.698 (95% CI, 0.588-0.807) for predicting the relapse of refractory moderate to severe CD, which was consistent with the results of previous studies. Although the AUC values were obtained from different cohorts with different study designs, the AUCs for the induction response and treatment persistence were similar.

Based on real-life data, Khorrami et al reported that the proportion of clinical failure after administration of loading dose of ustekinumab at 12.0 months was 36% (32 of 88 patients), and the proportion of clinical failure at the end of follow-up (median, 10.0 months; IQR, 5.0-21.0 months) was 42% (49 of 116 patients) in refractory CD.[17] Alric et al reported sustained corticosteroid-free remission rates at week 48 of 27.4% (29 of 107 patients), CD-related abdominal surgery rate at week 48 of 9.5% (10 of 107 patients), and hospitalization rate at week 48 of 24.1% (26 of 107 patients) in patients with refractory CD treated with ustekinumab in a real-life clinical setting.[18] In the subpopulation analysis of Japanese patients from UNITI-1, UNITI-2, and IM-UNITI, the clinical remission rate at week 44 was 50.0% (4 of 8 patients), which is consistent with that in the overall population[19]. Our study demonstrated that the clinical relapse rate of ustekinumab at the end of follow-up (median, 12.0 months; IQR, 6.0-22.0 months) was 37.4% (37 of 99 patients); CD-related surgery rate was 11.1% (11 of 99 patients); and CD-related hospitalization rate was 22.2% (22 of 99 patients) in Korean patients with refractory CD in a real-life clinical practice. We also showed that the previous use of vedolizumab and concomitant corticosteroids at ustekinumab initiation was independently associated with clinical relapse during ustekinumab treatment for moderate to severe CD. The use of concomitant corticosteroids during the biologic agent initiation phase has proved to be an independent negative predictor of ustekinumab response in patients with CD in a previous study, which was consistent with our results.[20] The use of steroids at treatment

Table 3. Clinical remission rates at week 20 and multivariable-adjusted odds ratios of clinical remission according to CDST-UST (N = 99).

Variables	Low Probability Responders (n = 20)	Intermediate Probability Responders (n = 39)	High Probability Responders (n = 40)	*P Trend
Clinical remission at week 20				
Events	5 (25.0%)	26 (66.7%)	30 (75.0%)	0.001
Multivariable-adjusted OR (95% confidence interval)[a]	(Reference)	4.052 (0.961-17.078)	4.437 (1.018-19.337)*	

Variables are expressed as n (%).
Multivariable model adjusted for age, sex, body mass index, disease duration, extraintestinal manifestation, CD location, perianal lesion, previous immunomodulator use, opioid use history, corticosteroid at initiation, immunomodulator at initiation, dose intensification, CDAI, and CRP.
Abbreviations: OR, odds ratio; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein
*P value < .05.

initiation reflects the severity of disease activity and is related to poor clinical treatment outcomes. Previous anti-TNF-α exposure was shown to be a significant independent risk factor for clinical relapse only in the univariate analysis but not in the multivariate analysis. However, previous use of vedolizumab was a significant independent risk factor for clinical relapse in the multivariate analysis. Because vedolizumab was granted a market approval after anti-TNF-α for a certain time in Korea, there might have been more intractable patients previously exposed to anti-TNF-α agents in the vedolizumab-treated group. Perianal lesions and concomitant immunomodulator use at ustekinumab initiation were not associated with clinical relapse in our study.

The strength of our study lies in the analysis of the maintenance outcomes of ustekinumab in Asian patients with CD. In addition, this is the first validation study on the usefulness of the UST-CDST with real-life patient data in terms of maintenance and induction. However, our study is not free from certain limitations. First, the sample size was relatively small. Second, this study had an innate limitation related to its retrospective design. Third, data on serum ustekinumab levels and anti-drug antibody levels were not available. In a previous study, the exposure-efficacy relationships of VDZ-CDST for vedolizumab were investigated.[10] Further studies are warranted to explore the exposure-efficacy relationship of UST-CDST for ustekinumab. Fourth, the previous vedolizumab use was not adjusted in this data set, although other various confounders such as age, sex, body mass index, disease duration, extraintestinal manifestation, CD location, perianal lesion, previous immunomodulator use, opioid use history, corticosteroid at initiation, immunomodulator at initiation, dose intensification, CDAI, and CRP were included for adjustment. It was found that the predictive power of UST-CDST after adding vedolizumab valuable was lower than that excluding the variable. In Korea, vedolizumab has been used as a second-line drug until recently, which can produce different results than when it is used as a first-line drug.

Conclusion

In conclusion, the UST-CDST can predict clinical relapse in patients with moderate to severe CD during ustekinumab maintenance in a real-life clinical practice. Optimal patients should be selected to reduce both the clinical failure of induction and relapse during ustekinumab therapy for CD using an appropriate clinical decision tool.

Funding

None.

Conflicts of interest

Nothing to declare.

Author Contributions

Development of the study concept and design: J.P., J.C., H.Y. and J.H.C. Study supervision: H.Y., and J.H.C. Acquisition of data: J.P., J.C., and H.Y. Data analysis and interpretation: J.P. Drafting of the manuscript: J.P. Critical revision of the manuscript for important intellectual content: J.C., H.Y., and J.H.C.

References

1. Barberio B, Savarino EV, Card T, et al. Incidence comparison of adverse events in patients with inflammatory bowel disease receiving different biologic agents: retrospective long-term evaluation. *Intest Res* 2022;20(1):114–123.
2. Hanauer SB, Sandborn WJ, Feagan BG, et al. IM-UNITI: three-year efficacy, safety, and immunogenicity of ustekinumab treatment of Crohn's disease. *J Crohns Colitis* 2020;14(1):23–32.
3. Gutierrez A, Rodriguez-Lago I. How to optimize treatment with ustekinumab in inflammatory bowel disease: lessons learned from clinical trials and real-world data. *Front Med (Lausanne)* 2021;8:640813.
4. Ito T. Long-term clinical effectiveness of ustekinumab in patients with Crohn's disease: a retrospective cohort study. *Crohn's & Colitis 360*. 2020;2(4).
5. Song EM, Yang SK. Natural history of inflammatory bowel disease: a comparison between the East and the West. *Intest Res* 2021;ir.2021.00104.
6. Shin SY, Park SJ, Kim Y, et al. Clinical outcomes and predictors of response for adalimumab in patients with moderately to severely active ulcerative colitis: a KASID prospective multicenter cohort study. *Intest Res* 2021;ir.2021.00049.
7. Gisbert JP, Chaparro M. Predictors of primary response to biologic treatment [Anti-TNF, Vedolizumab, and Ustekinumab] in patients with inflammatory bowel disease: from basic science to clinical practice. *J Crohns Colitis* 2020;14(5):694–709.
8. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. *Aliment Pharmacol Ther.* 2017;45(9):1232–1243.
9. Dulai PS, Boland BS, Singh S, et al. Development and validation of a scoring system to predict outcomes of vedolizumab treatment in patients with Crohn's disease. *Gastroenterology* 2018;155(3):687–695.e10.
10. Dulai PS, Amiot A, Peyrin-Biroulet L, et al. A clinical decision support tool may help to optimise vedolizumab therapy in Crohn's disease. *Aliment Pharmacol Ther.* 2020;51(5):553–564.
11. Alric H, Amiot A, Kirchgesner J, et al. Vedolizumab clinical decision support tool predicts efficacy of vedolizumab but not ustekinumab in refractory Crohn's disease. *Inflamm Bowel Dis.* 2022;28:218–225.

12. Dulai PS. Clinical prediction model and decision support tool for ustekinumab in Crohn's disease. *Am J Gastroenterol.* 2019;114:S373.
13. Roltgen K, Powell AE, Wirz OF, et al. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. *Sci Immunol.* 2020;5(54).
14. Doherty MK, Ding T, Koumpouras C, et al. Fecal microbiota signatures are associated with response to ustekinumab therapy among Crohn's disease patients. *mBio* 2018;9(2):e02120–17.
15. He M, Li C, Tang W, et al. Machine learning gene expression predicting model for ustekinumab response in patients with Crohn's disease. *Immun Inflamm Dis* 2021;9(4):1529–1540.
16. Lee SH, Walshe M, Oh EH, et al. Early changes in serum albumin predict clinical and endoscopic outcomes in patients with ulcerative colitis starting anti-TNF treatment. *Inflamm Bowel Dis.* 2021;27(9):1452–1461.
17. Khorrami S, Ginard D, Marin-Jimenez I, et al. Ustekinumab for the treatment of refractory Crohn's disease: the Spanish experience in a large multicentre open-label cohort. *Inflamm Bowel Dis.* 2016;22(7):1662–1669.
18. Alric H, Amiot A, Kirchgesner J, et al. The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor. *Aliment Pharmacol Ther.* 2020;51(10):948–957.
19. Hibi T, Imai Y, Murata Y, et al. Efficacy and safety of ustekinumab in Japanese patients with moderately to severely active Crohn's disease: a subpopulation analysis of phase 3 induction and maintenance studies. *Intest Res* 2017;15(4):475–486.
20. Hoffmann P, Krisam J, Wehling C, et al. Ustekinumab: "Real-world" outcomes and potential predictors of nonresponse in treatment-refractory Crohn's disease. *World J Gastroenterol.* 2019;25(31):4481–4492.