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# The effects of ustekinumab on small intestinal lesions and stenotic lesions

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## ABSTRACT

Crohn's disease patients suffer from symptoms originating from small bowel lesions, including strictures. As many of these patients also have a potential risk of surgery, it is important to consider various therapeutic strategies for small bowel lesions. We retrospectively analyzed the therapeutic effects of ustekinumab, interleukin-12 and -23 blocker, for small intestinal lesions and intestinal stenosis in order to contribute to the optimal management of Crohn's disease. Patients who underwent total colonoscopy or small bowel endoscopy before and after the introduction of ustekinumab were enrolled in this study. The colonoscopy findings were evaluated by the simple endoscopic score for Crohn's disease, and small bowel endoscopy findings were evaluated using the modified simple endoscopic score for Crohn's disease. Endoscopic scores were compared before and after the introduction of ustekinumab and between the responders and non-responders to ustekinumab. Responders were defined as those whose Crohn's disease activity index score at 24 weeks fell below 150 points, or those whose score decreased by more than 100 points from the pre-induction level. A total of 50 patients were enrolled in the study, and the number of responders was 35. Pre-induction simple endoscopic scores were lower for responders, but no significant difference was observed in the modified simple endoscopic scores. The total decrease in the endoscopic score was significantly higher in the responders for both the small and large intestine. Use of ustekinumab as a first-line treatment for patients with small bowel lesions or stricture-prone lesions may be a new treatment consideration in the future.

Keywords: Crohn's disease, small bowel endoscopy, stenotic small intestine lesion, total colonoscopy, ustekinumab

Abbreviations:
CD: Crohn's disease
DBE: double-balloon endoscopy
SES-CD: simple endoscopic score for Crohn's disease

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TNF: tumor necrosis factor
UST: ustekinumab



## INTRODUCTION

Crohn's disease (CD) is an idiopathic inflammatory bowel disease that occurs in the entire gastrointestinal tract, from the mouth to the anus, with repeated remissions and exacerbations.[1-3] Statistics show that approximately one-third of all patients with CD require surgery. Some of these patients require surgery for small intestinal lesions, including those in the terminal ileum, which is the primary site of the disease. In addition, stenotic lesions are also one of the main reasons for the need for surgery.[4] Therefore, the control of small intestinal lesions and management of stenotic lesions are considered to be crucial in the treatment of CD.[5] With the advent of anti-tumor necrosis factor (TNF) agents, the number of patients whose condition can be controlled is relatively higher than before.[6-7] However, there are still many patients who require surgery for small bowel lesions.[8] Therefore, the therapeutic effect of CD on small intestinal lesions has attracted much attention in recent years.[9,10] Although the first biologic (anti-TNF) agents are considered highly-effective drugs, it has been reported that their therapeutic effect on small intestinal lesions may be weaker than that on colorectal lesions.[11] As for stenotic lesions, there are still few reports on sufficient therapeutic effects.

Ustekinumab (UST) is the biologic that can be used after treatment with anti-TNF agents. UST has shown high efficacy and safety in both clinical trials and clinical practice.[12-14]

We previously reported that a low colonoscopy score (simple endoscopy score for Crohn's disease; SES-CD) was a predictor of a patient's response to UST. In that study, we assessed the small intestinal mucosal status of patients using our own small intestinal simple endoscopic score (Modified SES-CD).[15] We found that both responders and non-responders of UST did not differ at baseline in the Modified SES-CD for both the small and large bowels. In other words, the small intestinal mucosa may show a therapeutic effect. However, the number of cases is limited.

Therefore, in this study we increased the number of cases and evaluated the effects of UST on small bowel and stenotic lesions.

## MATERIALS AND METHODS

*Ethical considerations*

This retrospective study was conducted with the approval of the ethics committee of Nagoya University Hospital in Japan (research ID: 2015-0466). Informed consent was obtained from the website on the homepage of our department.

*Patients and study design*

We reviewed the medical charts of consecutive patients who received UST at Nagoya University Hospital from June 2017 to June 2021. Patients who had received the UST for at least 24 weeks were eligible for evaluation in this study (n = 100). As for the criteria for the use of UST, our facility holds a conference with the physician in charge and the team, and the final decision is made in consultation with the patient. Among them, patients (n = 50) who underwent total colonoscopy or double-balloon endoscopy (DBE) before and after treatment to evaluate the intestinal mucosa were enrolled (n = 50). We usually recommend evaluation of intestinal mucosa

by endoscopy in all patients, however, some patients may refuse for various reasons (oral and transanal DBE requires hospitalization for several days). Therefore, 50 cases were available for observation, and 50 cases were used for the study.

These patients had received a weight-range-based dose of approximately 6 mg of UST per kg of body weight every 8 weeks (260 mg of UST for patients with a weight ≤55 kg, 390 mg of UST for patients with a weight >55–85 kg, and 520 mg of UST for patients with a weight >85 kg). We retrospectively analyzed the continuation rate of the use of UST and therapeutic effects of long-term UST use.

We evaluated the therapeutic effect of UST by comparing the results of responders with those of non-responders. Responders were defined as those whose Crohn's disease activity index score at 24 weeks fell below 150 points, or those whose score decreased by more than 100 points from the pre-induction level. The others who did not meet these criteria were defined as non-responders. We compared the two groups and analyzed the changes in the patient's endoscopic scores due to the treatment effects. The primary endpoint was the change in disease activity in the small bowel due to the treatment effect, and the secondary endpoint was the degree of improvement in stenotic lesions. After the values of these factors before and after treatment were compared, we evaluated the changes in the state of the intestinal mucosa in response to treatment and the optimal state of the intestinal tract before treatment. From this evaluation, we analyzed the optimal intestinal conditions for UST treatment.

*SES-CD and Modified SES-CD*

Total colonoscopy or DBE was usually performed on eligible patients within 3 months before UST induction and was evaluated using the SES-CD score or modified SES-CD score. DBE was performed via both the oral and anal routes. In addition, in some cases, a total colonoscopy or DBE was performed 24–48 weeks after induction of UST to determine the effect of treatment and evaluated using the above score. For patients who underwent anal DBE, total colonoscopy was not performed as the colonic mucosa could also be evaluated via this route.

The SES-CD score, which is a colonoscopy score for CD, was evaluated in five segments including the pre-defined ileal end. The modified SES-CD is our own score for DBE based on a previous report in which the small intestine was evaluated in three sections.[15] Specifically, SES-CD scores the size and extent of ulcers, lesions other than ulcers, and stenotic lesions in each of the five areas of the ileum and total colon. Modified SES-CD is a score for mucosal observation using small bowel endoscopy, and was created by us. The small intestine is divided into three sections according to the distance from the end of the ileum, and the size and extent of ulcers, lesions other than ulcers, and stenotic lesions in each section are scored and added up. We further evaluated the whole small intestine via both routes using DBE. The endoscopic scores were determined by a single reader who was blinded to the clinical results.

*Statistical analysis*

The data analyses were performed with the statistical software package SPSS (SPSS Inc, Chicago, IL, USA). The data from the responders and non-responders were compared using the Mann–Whitney U test or $\chi^2$ test. In all analyses, a $P$ value $<0.05$ was considered statistically significant.

## RESULTS

*The effectiveness and safety of the long-term use of ustekinumab for Crohn's disease*

A total of 100 patients were administered UST for CD in our hospital from June 2017 to June 2021. The continuation rates of UST use for all patients are shown in Fig 1a. Among them, 90 patients continued to use UST for at least 24 weeks. The patient's demographics and baseline disease characteristics are shown in the Supplementary Table. The mean value of Crohn's disease activity index for all 90 eligible patients was 224.5 ± 93.0. The mean responder's (n = 62) score was 227.1 ± 99.3 and that of the non-responders (n = 28) was 218.7 ± 65.5. No significant differences between the two groups were observed. Of the 90 patients, 68.9% achieved a clinical response at week 24.

Only 50 patients of the total sample underwent endoscopic evaluation of the intestinal mucosa before and after treatment; therefore, only these patients were included in the analysis of the

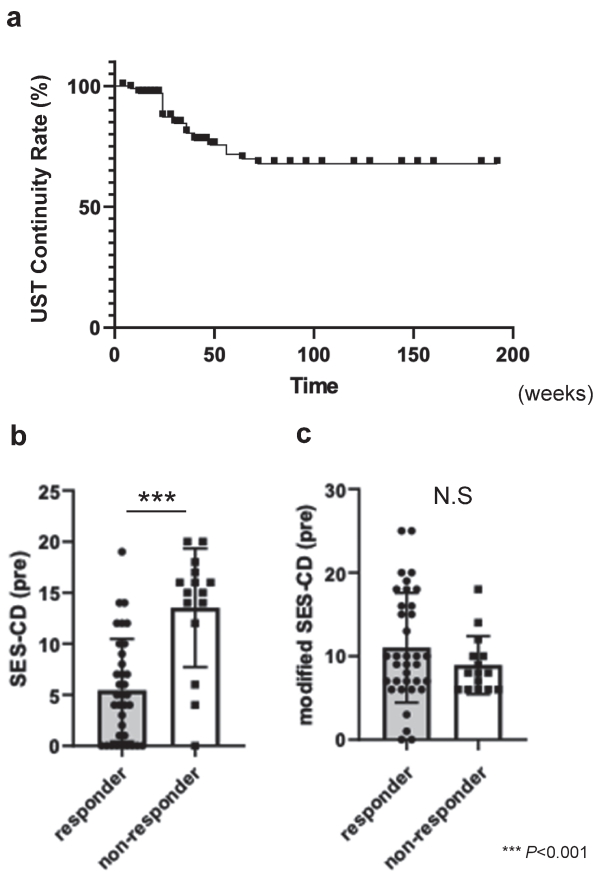


**Fig. 1** Patient's ustekinumab continuity rate and pre-treatment SES-CD

**Fig. 1a:** The continuous ustekinumab use rates for all patients (n = 100).

**Fig. 1b:** The comparison of the SES-CD for the responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 1c:** The comparison of the modified SES-CD for the responders (n = 35) and non-responders (n = 15) before the induction of UST.

SES-CD: simple endoscopic scores for Crohn's disease

UST: ustekinumab

N.S: no significant differences

*** $P$ <0.001

endoscopic score in this study (Table 1). Of those, 35 were male and 15 were female. The median age was 42 years (range 20–85), and the mean body weight was 48.3 kg (29.0–78.6). A total of 72% of the patients had been treated with at least one TNF-α antagonist, and 44% had been treated with two or more TNF-α antagonists; only 28% of the patients had not received any TNF-α antagonist.

The mean SES-CD score before UST induction in responders and non-responders was 6.1± 5.1 and 13.2 ± 5.3, respectively. This showed that the scores of the responders were significantly lower than those of the non-responders (Fig. 1b). There was no significant difference observed in the modified SES-CD between the two groups before the induction of UST (Fig. 1c). The mean stenotic score (a sub-score in the SES-CD measuring the appearance of narrowing) for the responders and non-responders was 1.3 ± 1.2 and 1.9 ± 1.2, respectively, with no significant difference observed between the two groups. Conversely, the scores of the ulcer size, ulcerated surface, and affected surface for the responders were 2.2 ± 2.0, 1.8 ± 1.5, and 0.7 ± 1.0, respectively, and for the non-responders were 5.3 ± 2.5, 4.7 ± 2.4, and 1.3 ± 1.2, respectively; the scores were all significantly lower for responders than for non-responders (Fig. 2a, 2b, 2c ,2d). Regarding the modified SES-CD, there were no significant differences observed between the responders and non-responders in all four sub-scores (Fig. 3a, 3b, 3c ,3d).

**Table 1** Comparison of patient background and laboratory data between responders (n = 35) and non-responders (n = 15) at baseline

| Characteristics | Responder (n = 35) | Non-responder (n = 15) | *P* |
|---|---|---|---|
| Male, % | 65.7 | 66.7 | 0.895** |
| Age, median, y | 45 | 35 | 0.059* |
| Weight, kg | 59.08 ± 10.05 | 54.20 ± 7.60 | 0.117* |
| BMI | 21.67± 3.48 | 21.83± 2.87 | 0.966* |
| CDAI | 214.91 ± 97.29 | 215.33 ± 79.94 | 0.958* |
| Median CRP, mg/L | 0.56 ± 0.71 | 0.75 ± 1.14 | 0.975* |
| Median Albumin, g/dL | 3.54 ± 0.59 | 3.44 ± 0.62 | 0.702* |
| Gastrointestinal areas involved, % (Montreal classification) | | | |
| L1 ileal (%) | 22.9 | 33.3 | 0.439** |
| L2 colonic (%) | 5.7 | 6.6 | 0.897** |
| L3 ileocolonic (%) | 71.4 | 60.0 | 0.427** |
| p perianal disease (%) | 45.7 | 53.3 | 0.621** |
| History of TNF antagonist treatment (%) | 71.4 | 80.0 | 0.527** |
| Patients who received 2 or 3 drugs (%) | 51.4 | 60.0 | 0.577** |

CDAI: Crohn's disease activity index
TNF: tumor necrosis factor
*Mann–Whitney *U* test
**Chi-squared test

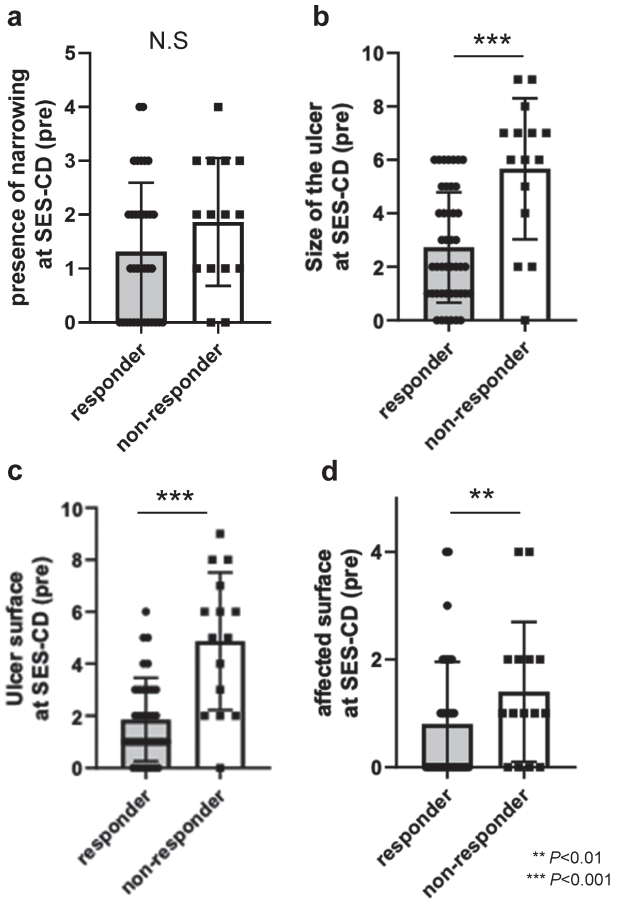


**Fig. 2** The comparisons of the SES-CD by each sub-section before the induction of UST

**Fig. 2a:** The comparison of the presence of narrowing in the SES-CD for the responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 2b:** The comparison of the size of the ulcer in the SES-CD for the responders (n = 35) and non-responder (n = 15) before UST induction.

**Fig. 2c:** The comparison of the ulcer surface in the SES-CD for responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 2d:** The comparison of the affected surface in the SES-CD of the responders (n = 35) and non-responders (n = 15) before UST induction.

SES-CD: simple endoscopic scores for Crohn's disease

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** $P$ <0.01

*** $P$ <0.001

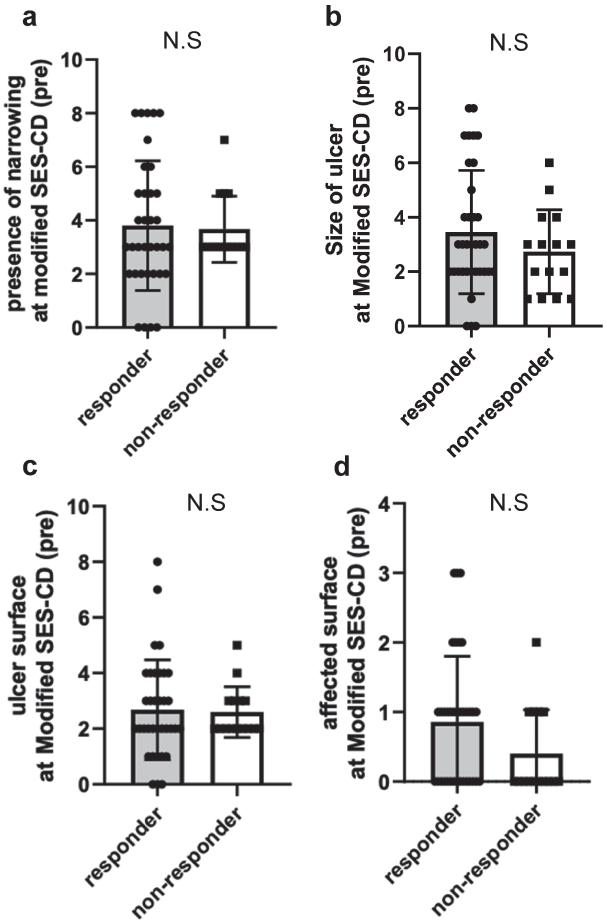


**Fig. 3** The comparison of the modified SES-CD by each sub-section before the induction of UST

**Fig. 3a:** The comparison of the presence of narrowing in the modified SES-CD of the responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 3b:** The comparison of the size of the ulcer in the modified SES-CD of the responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 3c:** The comparison of the ulcer surface in the modified SES-CD of the responders (n = 35) and non-responders (n = 15) before UST induction.

**Fig. 3d:** The comparison of the affected surface in the modified SES-CD of the responders (n = 35) and non-responders (n = 15) before UST induction.

SES-CD: simple endoscopic scores for Crohn's disease

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*The effectiveness of ustekinumab in the treatment of small intestinal lesions and colon in Crohn's disease evaluated in 50 cases*

The improvement change (a decrease in the total score is considered an improvement) of the endoscopic scores for responders on the SES-CD and modified SES-CD was 3.1 ± 3.7 and 7.0 ± 5.5, respectively; with a significant difference observed in the decrease of the overall score when compared to those of the non-responders (–0.2 ± 2.6 for SES-CD and 0.2 ± 3.2 for modified SES-CD; Fig. 4a, 4b).

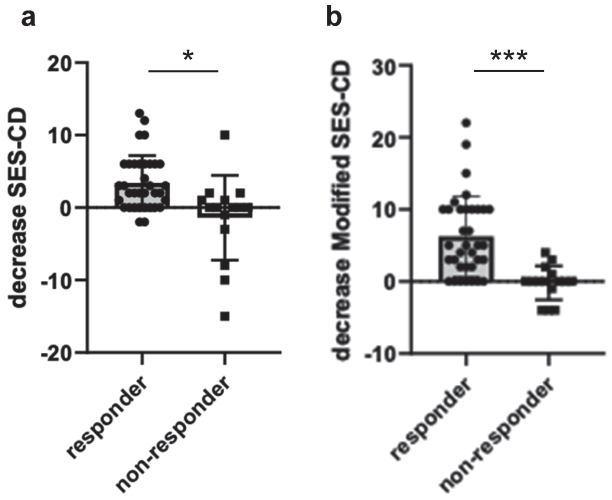


**Fig. 4** The comparison of the amount of decrease in the total SES-CD after the induction of UST

**Fig. 4a:** The comparison of the amount of decrease of the SES-CD between the responders (n = 35) and non-responders (n = 15) after the induction of UST.

**Fig. 4b:** The comparison of the amount of decrease of the modified SES-CD between the responders (n = 35) and non-responders (n = 15) after the induction of UST.

SES-CD: simple endoscopic scores for Crohn's disease

UST: ustekinumab

* $P$ <0.05

*** $P$ <0.001

*The effectiveness of ustekinumab for the treatment of CD patients with stenotic lesions*

A greater and more statistically significant decrease in the SES-CD sub scores for the presence of stenotic lesions and ulcer size was observed for responders (0.6 ± 0.8 and 1.1± 1.6) when compared to those for the non-responders (–0.6 ± 0.7 and 0.05 ± 1.5). There were no significant differences observed in the other sub scores (Fig 5a, 5b, 5c, 5d). Generally, the modified SES-CD's mean sub scores (presence of narrowing, size of ulcer, ulcer surface, and affected surface) were significantly lower for the responders than those for the non-responders (2.4 ± 1.8, 1.6 ± 1.8, 1.4 ± 1.6, 0.6 ± 0.7 and –0.1 ± 1.2, 0.1 ± 1.2, 0.2 ± 0.9, 0.2 ± 0.4, respectively) (Fig 6a, 6b, 6c, 6d). At least for stenotic lesions, there was a significant difference in responders compared with non-responders in both SES-CD and Modified SES-CD.

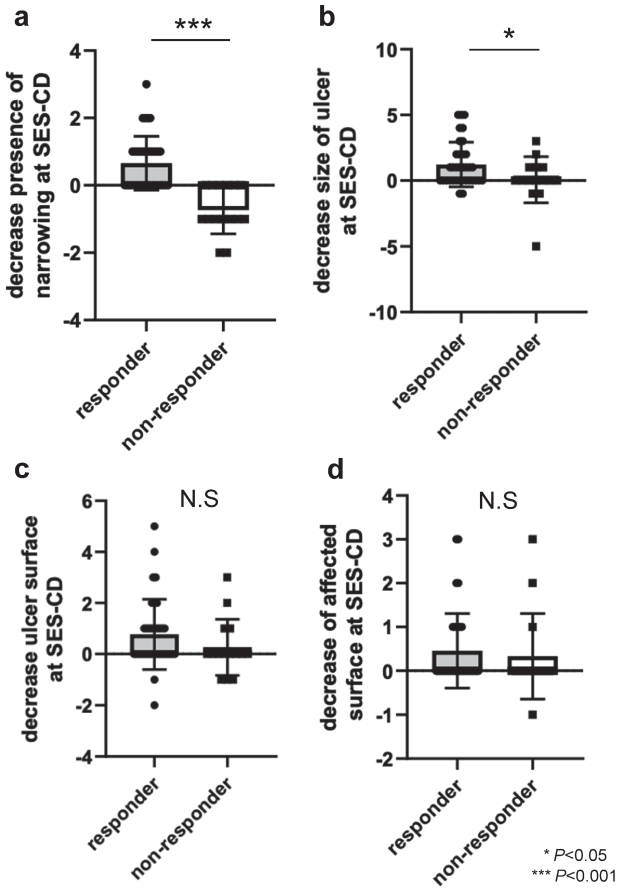


**Fig. 5** The comparison of the amount of decrease in the SES-CD by each sub-section after the induction of UST

**Fig. 5a:** The comparison of the reduction in the presence of narrowing in the SES-CD between the responders (n = 35) and non-responder (n = 15) after UST induction.

**Fig. 5b:** The comparison of the reduction of the size of the ulcer in the SES-CD between the responders and non-responders after UST induction.

**Fig. 5c:** The comparison of the reduction of the ulcer surface in the SES-CD between the responders (n = 35) and non-responders (n = 15) after UST induction.

**Fig. 5d:** The comparison of the reduction of affected surface in the SES-CD between the responders (n = 35) and non-responders (n = 15) after UST induction.

SES-CD: simple endoscopic scores for Crohn's disease

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* $P$ <0.05

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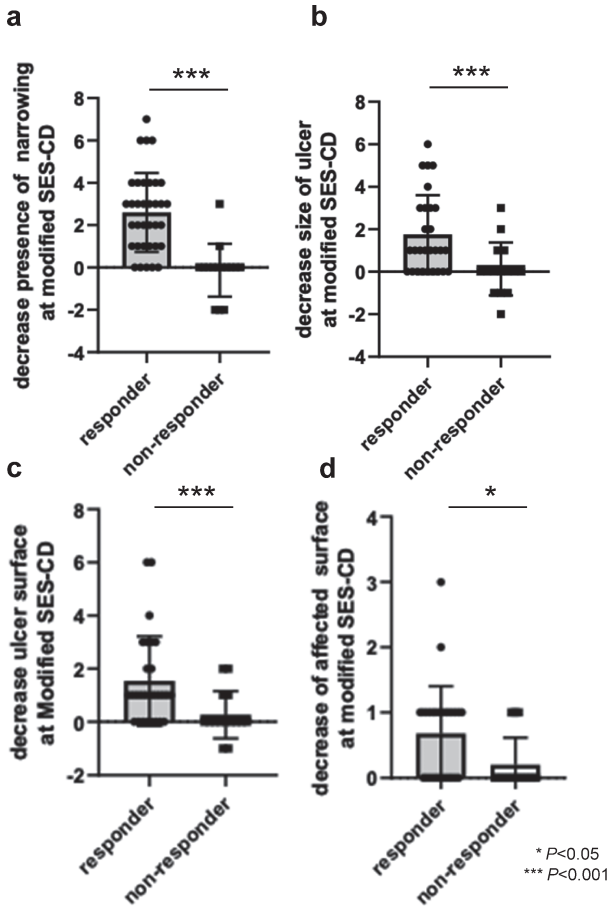


**Fig. 6** The comparison of the amount of decrease in the total modified SES-CD by each sub-section after the induction of UST

**Fig. 6a:** The comparison of the reduction of the presence of narrowing in the modified SES-CD between the responders (n = 35) and non-responders (n = 15) after UST induction.

**Fig. 6b:** The comparison of the reduction of the size of the ulcer in the modified SES-CD between the responders and non-responders after UST induction.

**Fig. 6c:** The comparison of the reduction of the ulcer surface in the modified SES-CD between the responders (n = 35) and non-responders (n = 15) after UST induction.

**Fig. 6d:** The comparison of the reduction of affected surface in the modified SES-CD between the responders (n = 35) and non-responders (n = 15) after UST induction.

SES-CD: simple endoscopic scores for Crohn's disease

UST: ustekinumab

* $P$ <0.05

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## DISCUSSION

In this study, we evaluated the clinical efficacy of UST and analyzed its clinical effects on the intestinal mucosa using endoscopy. As UST has been in use in clinical practice for approximately 4 years, its clinical effect and characteristics are becoming clearer.[16]

In this study, approximately 70% of patients obtained a clinical response. This result was

slightly higher than the results of other clinical trials and data from other countries. The reason for this is unclear, but it may be due to the 24-week evaluation period (which was based on our previous report).[15] Although there were some patients who were evaluated for a shorter period, we felt that the positive results observed were due to the 24-week evaluation period that allowed us to treat and evaluate these patients more appropriately. With that in mind, this study could serve as a reference for evaluating the disease activity during the clinical course of CD.

Moreover, the effect on small bowel lesions, including stricture, was analyzed according to the endoscopic score before and after treatment. These results showed that the lower the before treatment SES-CD score, the more effective the treatment; this result is similar to our previously reported results.[15]

Interestingly, the modified SES-CD did not show any significant differences in the pretreatment scores between responders and non-responders. This result suggests that the pretreatment endoscopic score in the small bowel does not affect the treatment effect of UST. When we evaluated the degree of improvement in the endoscopic score before and after treatment, a significantly greater improvement for responders was observed with the decrease in both the SES-CD and modified SES-CD scores when compared to non-responders. These results indicate that UST has a therapeutic effect on both small bowel and colorectal lesions. In other words, even if the modified SES-CD value is higher before treatment (high small intestine inflammation), a sufficient therapeutic effect may still be expected for small intestinal lesions. This result may contribute to the decision making regarding the treatment of small intestinal lesions in CD patients, as it has been previously reported that anti-TNF agents are less effective in treating small intestinal lesions than colorectal lesions.[11] Considering this, the findings that UST has a significant therapeutic effect on small intestinal mucosa, regardless of the pre-treatment small bowel endoscopy score, may play an important role in the selection of treatment for small intestinal lesions.

Our results also showed that UST was effective at the stenotic site in both the colon and the small intestine. Although the reason is not known at this time, we speculated that there were two possible causes for this. First, it may be due to the mechanism of the drug. Since UST is an antibody against p40, which is common to interleukin 12 and interleukin 23, it may control the T helper 1 and 17 pathways in a balanced manner.[17] The T helper 17 pathway is related to innate lymphoid cell type 3 that is common in the small intestine.[18] Furthermore, the T helper 17 pathway affects the balance of the matrix metalloproteinases (MMPs) and the tissue inhibitors of matrix metalloproteinases (TIMPs), which cannot be overlooked.[19] Additionally, the formation of fibrotic stenosis in the small intestine is currently thought to take place during the wound healing process, which is thought to be affected by the T helper 17 cells.[20] During the wound healing process, fibroblasts are transformed into myofibroblasts, and if this is followed by chronic inflammation, the myofibroblasts remain active instead of apoptotic.[21] UST may avoid the progression of fibrosis. Second, the speed of the UST's therapeutic effect may also be a factor, whereby the difference in the time taken to induce this effect may lead to a more balanced intestinal improvement.

We have previously reported a case of an improved stenotic lesion, without restenosis, after endoscopic balloon dilation of the small intestine with the induction of UST.[22] In this report, we discussed that one of the factors that could have led to the patient's improvement without stenosis was the therapeutic effect observed at the start of UST induction. As previously mentioned, UST is one of the safest biological drugs available. Further, clinical trials and real-world data have shown UST to have sufficient efficacy.[13] For these reasons, the European Crohn's and Colitis Organization (ECCO) guidelines also recognize the usefulness of USTs and have recommended their use.[23] However, the decision regarding how to use several kinds of biologics, and which one to use first, is currently difficult. This may be due to the lack of reports on the clinical

features of relatively new agents such as UST.

This study had several limitations. This was a retrospective study, and the pre- and post-treatment endoscopies were performed in only half of the patients who received UST. Therefore, future studies should be clinical trials with pre- and post-treatment endoscopy of all patients who underwent USTs.

In conclusion, the results of our current study demonstrate the positive therapeutic effect of UST on small bowel lesions and stenotic lesions. There are the other papers on UST that focused on the condition of intestinal mucosa, but we focused on the stricture, which is the main cause of surgery. Therefore we were able to understand the real effects, especially in CD patients with small bowel lesions.

We hope that our results will suggest new ways for the use of UST that are different from that of anti-TNF agents. In other words, UST should be used as a first-line treatment for patients that predominantly have small bowel lesions or for those with lesions that may cause stricture. The use of UST as a first-line treatment for patients who are immunocompromised, where safety considerations are crucial, is reasonable from the perspective of the treat-to-target concept. There are still many issues that require resolution, such as the appropriate timing to switch the biologics and the optimal index.[24,25] In addition, it was not clear from this study alone how many patients were actually able to avoid surgery by introduction of UST. In order to analyze this, we will probably need more cases and longer-term observation. And that is the part that is most interesting to us. Although this study cannot clarify this part, we would like to consider collaborative research with multiple institutions as a future challenge.

However, we hope that this study will help many CD patients with small bowel lesions and stenotic lesions by determining new therapeutic strategies; further research on therapeutic strategies for CD, including the optimal use of biologics, will be conducted.

## AUTHOR CONTRIBUTION

Hirotaka Wada and Kentaro Murate served as co-first authors and contributed equally to this work.

## DISCLOSURE AND CONFLICT OF INTEREST STATEMENT

Masanao Nakamura, Takeshi Yamamura and Tsunaki Sawada were supported by Janssen Pharmaceutical KK, which manufactured ustekinumab, in the form of lecture fee. Other authors have no COI to disclose.

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**Supplementary Table** Comparison of responders (n = 62) and non-responders (n = 28) in patient background and laboratory data at baseline for all 90 patients

| Characteristics | Responder (n = 62) | Non-responder (n = 28) | *P* |
|---|---|---|---|
| Male, % | 69.3 | 67.8 | 0.991** |
| Age, median, yr | 43 | 40 | 0.167* |
| Weight, kg | 57.16±9.69 | 53.46±7.06 | 0.059* |
| CDAI | 227.19±99.33 | 218.75±65.50 | 0.512* |
| Median CRP, mg/L | 0.58±0.87 | 0.61±0.89 | 0.872* |
| Median Albumin, g/dL | 3.54±0.62 | 3.51±0.51 | 0.948* |
| GI areas involved, % (Montreal classification) | | | |
| L1 ileal (%) | 20.9 | 28.5 | 0.659** |
| L2 colonic (%) | 6.5 | 14.2 | 0.659** |
| L3 ileocolonic (%) | 72.6 | 57.1 | 0.427** |
| p perianal disease (%) | 41.9 | 50.0 | 0.305** |
| History of TNF antagonist treatment (%) | 74.1 | 75.0 | 0.935** |
| Patients who received 2 or 3 drugs (%) | 53.2 | 57.1 | 0.730** |

*Mann–Whitney *U* test

**Chi-squared test