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ORIGINAL RESEARCH—CLINICAL

Early Sonographic Improvement Predicts Clinical Remission and Mucosal Healing With Molecular-Targeted Drugs in Ulcerative Colitis

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BACKGROUND AND AIMS: Predicting the efficacy of molecular-targeted drugs (MTDs) is an unmet need in the treatment of ulcerative colitis (UC). Intestinal ultrasound (IUS) can be used to safely and repeatedly assess UC activity. **METHODS:** Thirty-eight patients who started MTD therapy for active UC and underwent IUS at baseline and 3 months after starting therapy were analyzed. Steroid-free clinical remission (SFCR) and endoscopic improvement (EI) at 6 months were defined as a Lichtiger index of $\leq$3 and Mayo endoscopic subscore of $\leq$1 while continuing the MTD without steroid induction or surgery. Sonographically estimated EI (SE-EI) at 3 months was assessed based on a Milan Ultrasound Criterion of $\leq$6.2 and Kyorin Ultrasound Criterion for UC (bowel wall thickness of $<$3.8 mm and submucosa index of $<$50%). **RESULTS:** Thirty-one patients achieved SFCR at 6 months [SFCR(+) group]. The SFCR(+) group demonstrated significantly better improvement in bowel wall thickness and bowel wall vascularity at 3 months than the SFCR(−) group. The Milan Ultrasound Criterion and UC-IUS index also improved significantly more in the SFCR(+) than SFCR(−) group. The areas under the curve of these parameters for predicting SFCR were approximately 0.80. Colonoscopy was performed for 28 patients at 6 months, and 15 patients achieved EI. SE-EI at 3 months was significantly associated with achievement of EI at 6 months. The positive predictive values of SE-EI at 3 months for SFCR and EI at 6 months were 100%. **CONCLUSION:** Sonographic improvements in 3 months predicted the clinical and endoscopic efficacy of MTD therapy at 6 months, suggesting the longitudinal significance of IUS monitoring for UC treatment.

Keywords: Intestinal Ultrasound; Ulcerative Colitis; Clinical Remission; Endoscopic Improvement; Molecular-Targeted Drug

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder characterized by colonic inflammation with periods of remission and relapse. The prognosis of UC has improved with advances in therapeutic options, including molecular-targeted drugs (MTDs).[1] The treat-to-target strategy is now widely accepted to achieve a better prognosis in patients with UC,[2] and both clinical and endoscopic improvement and remission are considered therapeutic targets in the clinical setting. Colonoscopy (CS) is the gold standard assessment technique for UC disease activity. Achieving endoscopic improvement (EI), defined as a Mayo endoscopic subscore (MES)[3] of 0 or 1, at approximately 6 months after starting remission induction therapy, is considered a clinical target for a better long-term prognosis of UC.[2,4–6] The ability to predict the clinical efficacy early after starting treatment, including EI at 6 months, would contribute to better clinical outcomes and reduce sociomedical costs because physicians could decide to continue or switch a medication earlier. Predicting the efficacy of an MTD is a crucial unmet need in UC treatment.

We hypothesized that intestinal ultrasound (IUS) early after beginning remission induction therapy with an MTD has the potential to predict efficacy at 6 months. IUS is considered a promising monitoring tool for UC. Whereas CS with pretreatment using laxatives can be invasive for patients, IUS is noninvasive and can be performed safely and repeatedly even for patients with active UC. IUS can be used to assess the whole colon and evaluate the disease distribution of UC.[7] Additionally, various cross-sectional studies have demonstrated that several IUS findings are associated with colonic inflammation and that some sonographic findings and scoring systems can estimate EI.[8–14] Bowel wall thickness (BWT), bowel wall vascularity [or bowel wall flow (BWF)], bowel wall stratification (BWS), colon haustration, and inflammatory mesenteric fat are widely used sonographic parameters for assessing UC disease activity.[8]

Abbreviations used in this paper: **BWF, bowel wall flow; BWS, bowel wall stratification; BWT, bowel wall thickness; CS, colonoscopy; EI, endoscopic improvement; IQR, interquartile range; IUS, intestinal ultrasound; KUC-UC, Kyorin Ultrasound Criterion for UC; LI, Lichtiger index; MES, Mayo endoscopic subscore; mLS, modified Limberg score; MTD, molecular-targeted drug; MUC, Milan Ultrasound Criterion; PPV, positive predictive value; SE-EI, sonographically estimated endoscopic improvement; SFCR, steroid-free clinical remission; SMI, submucosa index; SMT, submucosa thickness; UC, ulcerative colitis; UII, UC-IUS index.**

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Allocca et al[10,11] developed the Milan Ultrasound Criterion (MUC) using BWT and BWF and demonstrated that an MUC of ≤6.2 can estimate EI. Bots et al[12] showed that their UC-IUS index (UII) using BWT, BWF, haustration, and inflammatory mesenteric fat was well correlated with the MES. We developed the submucosa index (SMI), a new parameter based on BWT and submucosa thickness (SMT), and reported that the combination of BWT and the SMI can be used as a criterion to estimate EI [Kyorin Ultrasound Criterion for UC (KUC-UC): BWT of <3.8 mm and SMI of <50%].[13,14] Thus, evidence regarding the potential of IUS to estimate EI has accumulated.

In the present study, we investigated the clinical significance of IUS monitoring in MTD therapy. We found that the improvement of IUS findings at 3 months after starting induction therapy with an MTD predicts steroid-free clinical remission (SFCR) at 6 months of MTD therapy and demonstrated that achieving sonographically estimated EI (SE-EI) under IUS at 3 months leads to the achievement of EI under CS at 6 months.

Methods

Study Design and Patients

In this single-center retrospective study, we applied the following inclusion criteria to patients with UC: (1) an MTD was started as induction therapy for active UC, defined as a Lichtiger index (LI)[15,16] of ≥4, at Kyorin University Hospital (Tokyo, Japan) from September 2020 to June 2023, and (2) IUS was performed at baseline and 2–4 months after starting an MTD, and the MTD was continued at least until the second IUS. The patients satisfying the inclusion criteria were consecutively enrolled in the analyses. The diagnosis of UC was based on the Inflammatory Bowel Disease Guidelines of the Japanese Society of Gastroenterology.[17] The following clinical information was obtained from the hospital's medical record system: endoscopic and IUS findings, age at the time of examination, sex, disease duration, disease type, and therapeutic drugs.

Sonographic and Endoscopic Assessment

On transabdominal IUS, we assessed BWT, BWS including SMI, haustration, and inflammatory mesenteric fat using B-mode at the most severely affected segment of the colon. BWS was categorized as maintained, unclear, or loss of stratification. The SMI was defined as the percentage of SMT within the BWT (ie, SMI = 100 × SMT/BWT).[13,14] The SMI was recorded as 0 if the SMT was too thin to measure and was recorded as "undetermined" when the submucosa was unclear or could not be identified even with a BWT of >3 mm.[13,14] BWF was evaluated at the site where we measured BWT using the modified Limberg score (mLS) in color Doppler mode as follows: score of 0 = BWT of <3 mm and no color Doppler signal, score of 1 = BWT of ≥3 mm and no color Doppler signal, score of 2 = point-like short color Doppler signal, score of 3 = linear-appearing Doppler signal; and score of 4 = long color Doppler signal extending through the bowel wall and mesenteric tissue.[7,18] Based on the IUS findings, the MUC[10,11] and UII[12] were calculated as described in the original reports. An MUC cutoff value of 6.2 was employed to estimate EI.[11] We also assessed the use of our KUC-UC (BWT of <3.8 mm and SMI of <50%) for estimating EI.[13,14] Sonographic changes 3 months after starting MTD therapy were calculated and assessed based on the evaluation described above. A Canon Aplio i800 ultrasound system (Canon Medical Systems, Otawara, Japan) with a 6-MHz convex probe was used for all examinations. The velocity range of the color Doppler was set at 4.2 cm/s. The manufacturer's preset parameters for bowel examinations were used. Each IUS finding was confirmed by agreement among 3 examiners (J.M., H.M., and H.Y.), one of whom (J.M.) had completed the IUS training curriculum provided by the International Bowel Ultrasound Group (https://ibus-group.org/). Multiple examiners among the 3 examiners perform IUS together for patients with UC or other diseases and discuss and determine the IUS findings during the examination at our institution. Inflammatory bowel disease specialists independently performed CS or sigmoidoscopy (when deep insertion was considered high risk with severe activity or pain during the examination) and scored the disease activity using the MES[3] for the most severely affected segment. EI was defined as an MES of ≤1. Achievement of EI at 6 months was defined as an MES of ≤1 at 6 months with continuation of the MTD started for the induction therapy.

Table 1. Clinical Demographics

Number of patients	38
Sex, female/male	13/25
Age at induction therapy, y	34.5 (22–52.5)
UC disease duration, y	3.5 (1.2–9.8)
UC disease type, pancolitis/left sided	28/10
Lichtiger index at baseline	8 (6–9)
MES at baseline	2.5 (2–3)
MTD for induction therapy	
Adalimumab	2
Golimumab	1
Infliximab	8
Ustekinumab	13
Vedolizumab	5
Filgotinib	2
Tofacitinib	3
Upadacitinib	4
Concomitant medications	
5-aminosalicylic acid	21
Predonisolone	12
Azathioprine	7
Past use of MTD[a]	
None (naïve)	22
Adalimumab	2
Golimumab	1
Infliximab	7
Ustekinumab	4
Vedolizumab	7
Tofacinib	2
Cyclosporine	2
Taclorimus	1
Carotegrast methyl	1

Data are presented as n or median (interquartile range).
[a]Seven patients were treated with multiple molecular-targeted drugs before the current induction treatment.

Clinical Assessment

Clinical remission was defined as an LI of $\leq$3. SFCR at 6 months after starting MTD therapy was defined as an LI of $\leq$3 without terminating the MTD (ie, switching to other medications), undergoing surgery because of insufficient control of UC disease activity, or starting steroid induction therapy before 6 months.

Statistical Analysis

Continuous and categorical variables are presented as mean $\pm$ standard error and median with interquartile range (IQR), respectively. The Mann–Whitney *U* test was used for comparisons between the 2 groups. Fisher's exact test was used to analyze contingency tables. A receiver operating characteristic analysis was employed to evaluate the predictive ability of IUS findings and scoring systems for the clinical efficacy of an MTD.

Ethics

This study was approved by the Institutional Ethics Committee of Kyorin University School of Medicine (Approval Number 2264) and conducted in accordance with the Declaration of Helsinki. This study used recorded data, and the ethics committee approved a waiver for informed consent.

Results

Patient Demographics

Thirty-eight patients were analyzed (Table 1). Among these 38 patients, 28 had pancolitis and 10 had left-sided colitis. The MTD used for remission induction therapy was adalimumab, golimumab, infliximab, ustekinumab, vedolizumab, filgotinib, tofacitinib, and upadacitinib in 2, 1, 8, 13, 5, 2, 3, and 4 patients, respectively. Each patient continued the MTD without steroids or other MTDs for at least 3 months when IUS monitoring was performed. The median baseline LI of the 38 patients was 8 (IQR: 6–9). All patients showed endoscopically active colitis [MES of $\geq$2 (median: 2.5, IQR: 2–3)] at the baseline CS performed before starting MTD therapy (median: −2 weeks, IQR: −4 to 0 weeks). The sonographic and endoscopic findings at the baseline are shown in Table A1.

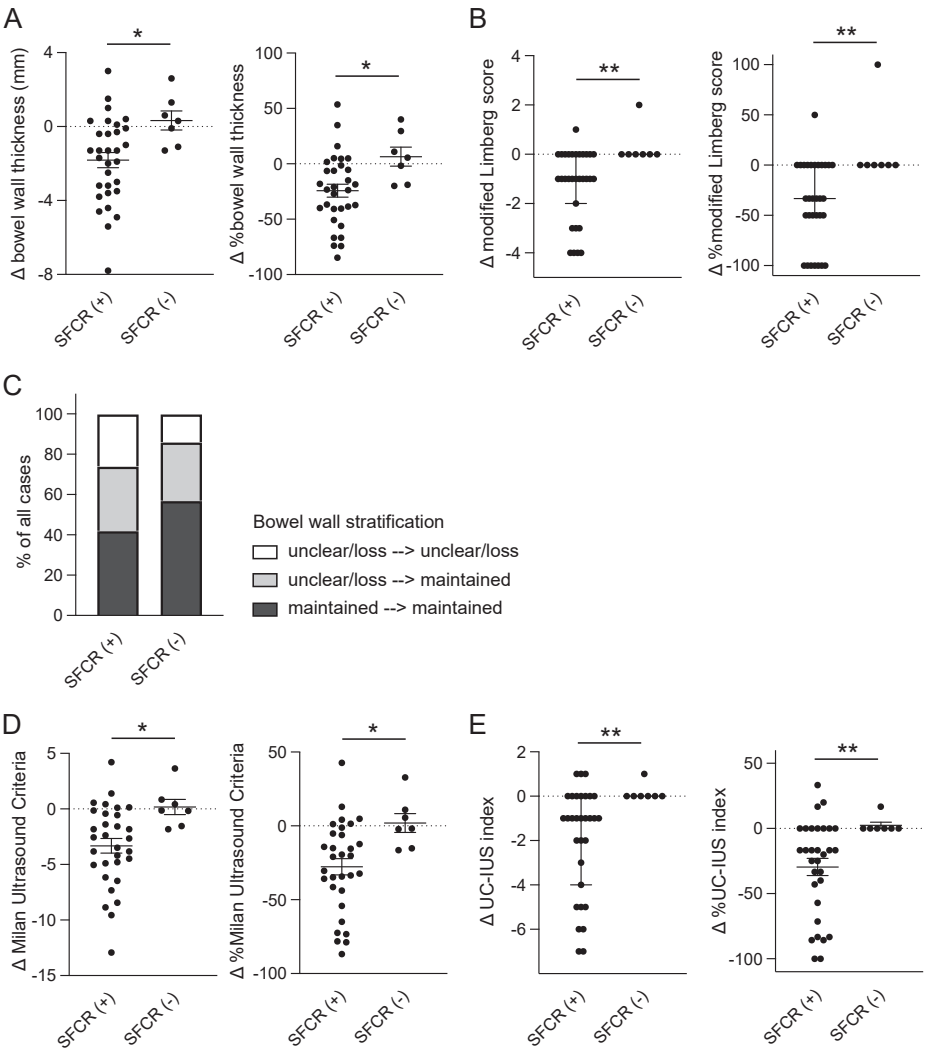

Figure 1. Changes in intestinal sonographic findings at 3 months and achievement of SFCR at 6 months after starting a molecular-targeted drug. The changes (Δ) in intestinal sonographic findings at 3 months with a molecular-targeted drug were compared between patients who did and did not achieve SFCR at 6 months. In calculating Δ%, the value at baseline was defined as 100%. (A) ΔBowel wall thickness (mm) and Δ%bowel wall thickness. (B) ΔModified Limberg score (mLS) and Δ%mLS. (C) Proportions of patients with each change pattern of bowel wall stratification. (D) ΔMilan Ultrasound Criterion and Δ%Milan Ultrasound Criterion. (E) ΔUC-IUS index and Δ%UC-IUS index. *P < .05 and **P < .01 with Mann–Whitney *U* test. IUS, intestinal ultrasound; SFCR, steroid-free clinical remission; UC, ulcerative colitis.

Sonographic Improvement During Induction Period and Achievement of SFCR

Among the 38 patients, 31 (81.6%) achieved SFCR at 6 months [SFCR(+) group]. The baseline IUS was performed when starting MTD therapy (median: 0 weeks, IQR: −1 to 0 weeks). Monitoring IUS was performed at 3 months (median: 13 weeks, IQR: 12–14.7 weeks) after induction of MTD therapy. The sonographic changes at 3 months were compared between the SFCR(+) and SFCR(−) groups. The change in BWT (ΔBWT) was −1.8 ± 0.4 mm in the SFCR(+) group and 0.3 ± 0.5 mm in the SFCR(−) group ($P = .0137$). Given the differences in the absolute value of BWT at baseline among the patients, the change in %BWT (Δ%BWT) (the baseline value was defined as 100%) was also assessed. The SFCR(+) and SFCR(−) groups showed a Δ%BWT of −24.3% ± 5.8% and 6.5% ± 8.6%, respectively ($P = .0149$) (Figure 1A). The change in mLS (ΔmLS) was −1 (IQR: −2 to 0) in the SFCR(+) group and 0 (IQR: 0–0) in the SFCR(−) group ($P = .0041$). The Δ%mLS was −37.1% ± 7.4% and 14.3% ± 14.3% in the SFCR(+) and SFCR(−) groups, respectively ($P = .0044$) (Figure 1B). The changes in BWS are presented in Figure 1C. There was no clear difference in the proportion of patients showing apparent improvement of BWS (ie, change from unclear/loss of stratification to maintained stratification) between the SFCR(+) group (32.3%) and SFCR(−) group (28.6%). The change in MUC (ΔMUC) was −3.32 ± 0.66 and 0.17 ± 0.68 in the SFCR(+) and SFCR(−) groups, respectively ($P = .0102$). The change in % MUC (Δ%MUC) was also evaluated. The SFCR(+) and SFCR(−) groups demonstrated an Δ%MUC of −27.7% ± 5.5% and 1.9% ± 6.4%, respectively ($P = .0135$) (Figure 1D). The change in UII (ΔUII) was −1 (IQR: −4 to 0) and 0 (IQR: 0–0) in the SFCR(+) and SFCR(−) groups, respectively ($P = .0063$). The Δ%UII was −29.6% ± 6.6% and 2.4% ± 2.4% in the SFCR(+) and SFCR(−) groups, respectively ($P = .0082$) (Figure 1E). The changes in sonographic findings among the SFCR(+) and SFCR(−) groups are also presented in Table A2. Receiver operating characteristic analyses for SFCR demonstrated a considerable area under the curve (95% confidence interval) for ΔBWT of 0.795 (0.642–0.948), Δ%BWT of 0.793 (0.632–0.953), ΔmLS of 0.820 (0.684–0.957), Δ%mLS of 0.820 (0.684–0.957), ΔMUC of 0.807 (0.665–0.948), Δ% MUC of 0.797 (0.646–0.948), ΔUII of 0.813 (0.681–0.945), and Δ%UII of 0.809 (0.676–0.941) (Figure A1). All patients with an MUC of ≤6.2 (n = 8), KUC-UC (n = 7), and MUC of ≤6.2, and/or KUC-UC [n = 9 (6 with MUC of ≤6.2 and KUC-UC, 2 with MUC of ≤6.2, and 1 with KUC-UC)] at 3 months (ie, SE-EI at 3 months) achieved SFCR at 6 months (Table 2). However, the association between SE-EI at 3 months and SFCR at 6 months was not statistically significant.

Sonographic Improvement During Induction Period and Achievement of Endoscopic Healing

Among the 38 patients, 28 underwent CS at approximately 6 months (median: 28 weeks, IQR: 26–29.5 weeks) with continuation of the MTD started at baseline. Total CS was performed for these patients, and 15 achieved EI [EI(+) group]. Sonographic changes at 3 months were compared between patients with and without achievement of EI at 6 months [EI(+) vs EI (−) groups]. There was no significant difference in ΔBWT (−2.1 ± 0.5 vs −0.7 ± 0.5 mm) or Δ% BWT (−31.0% ± 7.7% vs −8.3% ± 6.8%) between the groups (Figure 2A). The ΔmLS was −1 (IQR: −3 to 0) in the EI(+) group and 0 (IQR: −1 to 0) in the EI(−) group ($P = .0372$). The Δ%mLS was −44.4% ± 12.5% and −11.54% ± 5.1% in the EI(+) and EI(−) groups, respectively ($P = .0300$) (Figure 2B). The changes in BWS are presented in Figure 2C. A larger proportion of patients showed apparent improvement of BWS in the EI(+) group (40.0%) than in the EI(−) group (15.3%). The ΔMUC was −3.86 ± 0.88 and −1.18 ± 0.66 in the EI(+) and EI(−) groups, respectively ($P = .0476$). The EI(+) and EI(−) groups demonstrated an Δ%MUC of −34.3% ± 7.9% and −8.2% ± 5.7%, respectively ($P = .0325$) (Figure 2D). The ΔUII was −1 (IQR: −5 to 0) and 0 (IQR: −0.5 to 0) in the EI(+) and EI(−) groups, respectively ($P = .0075$). The Δ%UII was −38.2% ± 10.3% and −1.0% ± 4.5% in the EI(+) and EI(−) groups, respectively ($P = .0050$) (Figure 2E). The changes in sonographic findings among the EI(+) and EI(−) groups are also presented in Table A3. The area under the curve (95% confidence interval) for EI at 6 months was 0.685 (0.484–0.886) for ΔBWT, 0.718 (0.525–0.911) for Δ%BWT, 0.718 (0.523–0.913) for ΔmLS, 0.726 (0.531–0.920) for Δ%mLS, 0.721 (0.527–0.914) for ΔMUC, 0.739 (0.548–0.928) for Δ%MUC, 0.780 (0.605–0.954) for ΔUII, and 0.795 (0.627–0.963) for Δ%UII

Table 2. SE-EI at 3 Months and Achievement of SFCR at 6 Months With a Molecular-Targeted Drug

(1) SE-EI based on MUC of ≤6.2

		SFCR at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	8	0
	(−)	23	7

(2) SE-EI based on KUC-UC

		SFCR at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	7	0
	(−)	24	7

(3) SE-EI based on MUC of ≤6.2 and/or KUC-UC

		SFCR at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	9	0
	(−)	22	7

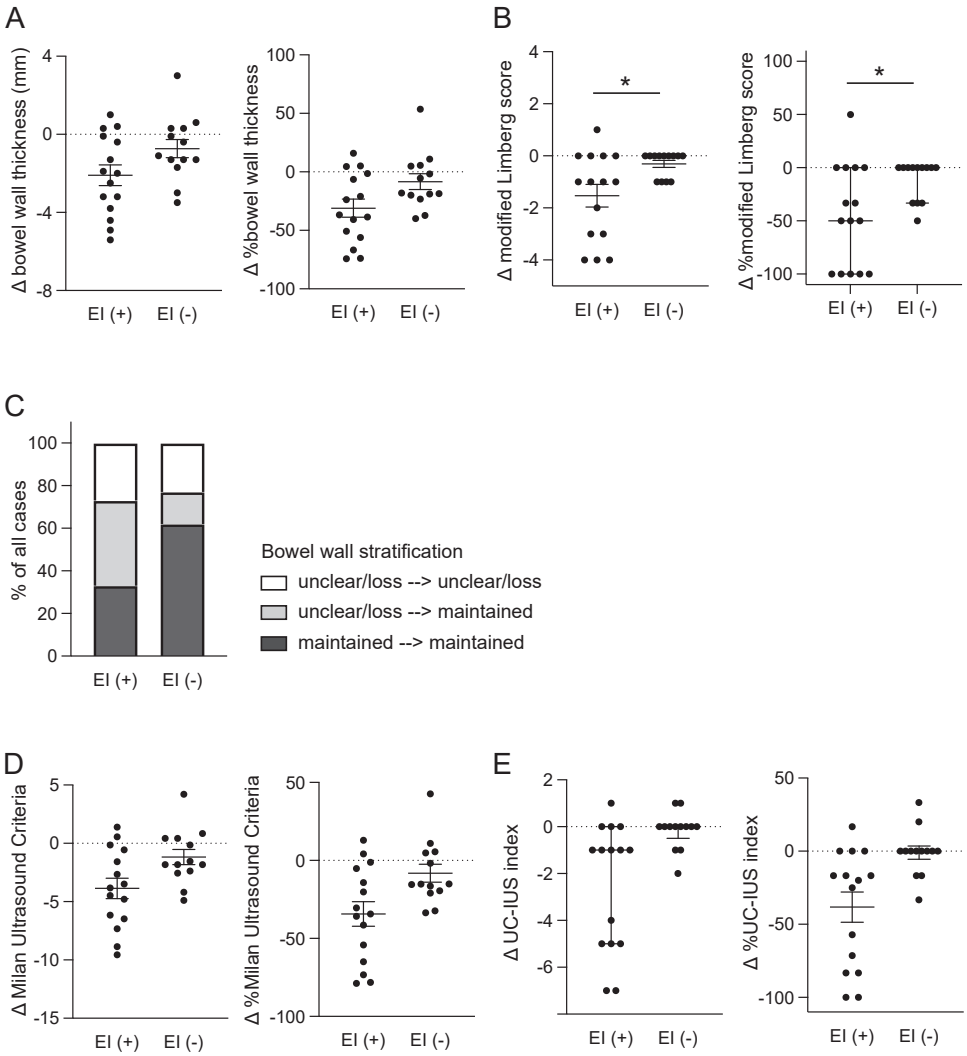

Figure 2. Changes in intestinal sonographic findings in 3 months and achievement of EI at 6 months after starting a molecular-targeted drug. The changes (Δ) in intestinal sonographic findings at 3 months with a molecular-targeted drug were compared between patients who did and did not achieve EI (Mayo endoscopic subscore of ≤1) at 6 months. (A) ΔBowel wall thickness (mm) and Δ%bowel wall thickness. The bowel wall thickness at baseline was defined as 100% in calculating Δ%bowel wall thickness. (B) ΔModified Limberg score and Δ%modified Limberg score. The modified Limberg score at baseline was defined as 100% in calculating Δ%modified Limberg score. (C) Proportions of patients with each change pattern of bowel wall stratification (unclear/loss to unclear/loss, unclear/loss to maintained, and maintained to maintained). (D) ΔMilan Ultrasound Criterion and Δ%Milan Ultrasound Criterion. (E) ΔUC-IUS index and Δ%UC-IUS index. *$P < .05$ with Mann-Whitney *U* test. EI, endoscopic improvement; IUS, intestinal ultrasound; UC, ulcerative colitis.

(Figure A2). Among the 28 patients, 5 demonstrated an MUC of ≤6.2, 5 satisfied the KUC-UC, and 6 achieved an MUC of ≤6.2 and/or KUC-UC (4 with both MUC of ≤6.2 and KUC-UC, 1 with MUC of ≤6.2, and 1 with KUC-UC) at 3 months. There was a significant association between SE-EI at 3 months and the achievement of EI at 6 months ($P = .0437$ for MUC, $P = .0437$ for KUC-UC, and $P = .0178$ for MUC/KUC-UC). The positive predictive value (PPV) of SE-EI at 3 months was 100% for EI at 6 months (Table 3).

Discussion

In the present study, improvement of IUS findings in 3 months and achievement of SE-EI at 3 months predicted the clinical and endoscopic efficacy of MTD therapy at 6 months. Our results suggest that achieving "sonographic improvement," defined using sonographic findings and scoring systems, can contribute to the clinical decision regarding whether to continue an MTD or switch to another MTD. EI is considered a more crucial target than SFCR for a preferable prognosis.[2] Notably, our study showed that SE-EI at 3 months was significantly associated with EI at 6 months, with a PPV of 100%. This finding suggests that achieving SE-EI at 3 months can support the treatment plan to continue an MTD but also provide an opportunity to reconsider the timing of CS, which is commonly performed at approximately 6 months to assess the MTD efficacy for UC. That is, the burden of endoscopic examination for evaluating the

Table 3. SE-EI at 3 Months and Achievement of EI at 6 Months With a Molecular-Targeted Drug

(1) SE-EI based on MUC of ≤6.2

		EI at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	5	0
	(−)	10	13
Sensitivity: 33.3% (95% CI: 15.2%–58.2%)			
Specificity: 100% (95% CI: 77.2%–100%)			
Positive predictive value: 100% (95% CI: 56.6%–100%)			
Negative predictive value: 56.5% (95% CI: 36.8%–74.3%)			

(2) SE-EI based on KUC-UC

		EI at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	5	0
	(−)	10	13
Sensitivity: 33.3% (95% CI: 15.2%–58.2%)			
Specificity: 100% (95% CI: 77.2%–100%)			
Positive predictive value: 100% (95% CI: 56.6%–100%)			
Negative predictive value: 56.5% (95% CI: 36.8%–74.3%)			

(3) SE-EI based on MUC of ≤6.2 and/or KUC-UC

		EI at 6 mo	
	Achievement (+)/(−)	(+)	(−)
SE-EI at 3 mo	(+)	6	0
	(−)	9	13
Sensitivity: 40.0% (95% CI: 19.8%–64.3%)			
Specificity: 100% (95% CI: 77.2%–100%)			
Positive predictive value: 100% (95% CI: 61.0%–100%)			
Negative predictive value: 59.1% (95% CI: 38.7%–76.7%)			

CI, confidence interval.

inflammatory condition at 6 months could be avoided in a well-responder who achieves SE-EI at as early as 3 months. Meanwhile, it also should be noted that not achieving SE-EI at 3 months does not mean a patient will fail to achieve EI. Our results also suggest that employing multiple IUS parameters and scoring systems can improve the predictive ability of IUS for UC disease activity. Although evidence for surveillance of UC-associated neoplasia with IUS has not been established, we believe that CS to survey UC-associated neoplasia should be performed even in patients with SE-EI. The clinical purpose and significance of CS and IUS must be considered for each patient.

Our findings underscore the importance of addressing 2 new clinical challenges: developing a practical, predictive IUS scoring system for MTD efficacy for clinical decision-making and establishing the appropriate timing of CS for patients who achieve SE-EI at 3 months. Follow-up CS should not be hastily postponed for patient safety because patients who require endoscopic assessment may be overlooked. However, balancing this with the need to reduce patients' burdens and conserve medical resources is a significant clinical challenge. Therefore, given that several sonographic parameters seemed to be promising predictors in this study and that the MUC and KUC-UC were originally developed for estimating EI but not predicting outcomes, developing a new scoring system specifically for predicting both SFCR and EI could contribute to improving the UC treatment strategy. Allocca et al[19] recently reported that an MUC of ≤6.2 at 12 weeks after starting biologics could predict the endoscopic response. The average follow-up timing of CS was 9.40 months (standard deviation: 3.59) and the PPV of an MUC of ≤6.2 for an MES of ≤1 was 67% in their study.[19] Given that several statements and guidelines recommend CS at 3–6 months after induction therapy,[4,6] our study suggests that patients who achieve SE-EI at 3 months can postpone the follow-up CS to assess the inflammatory condition later than recommended; the above-mentioned study[19] seems to support this notion. Because the PPV of an MUC of ≤6.2 for an MES of ≤1 was 100% in our study but 67% in their study, we cannot exclude the possibility that some patients with SE-EI at 3 months will develop endoscopic relapse later than 6 months.

The present study has some limitations. First, this was a retrospective study that included several MTDs. Although various types of MTDs achieved SE-EI in 3 months, the appropriate timing of IUS for monitoring the drug response may vary between MTDs. A future study in which each MTD is analyzed and IUS is performed at various time points will provide insights into the best timing of IUS for each medication. It is a crucial clinical challenge to examine if IUS at an earlier time point can predict the treatment efficacy. Also, serial IUS assessments up to 6 months could contribute to understanding the late responders to each MTD in UC treatment. However, this study reflects the real-world clinical setting, and approximately 3 months after starting an MTD seems to be a reasonable time to evaluate the efficacy of induction therapy in the clinical setting. Assessing IUS findings at a common time point regardless of the drug could be practical and easy for physicians to understand. Second, we employed transabdominal IUS, and proctitis was not analyzed in this study. Because the number of patients with proctitis treated with MTDs may be smaller than that of patients with other types of UC, our results still have relevance to inflammatory bowel disease clinical practice. Given that early peritoneal IUS showed a predictive potential for the short-term clinical response in UC,[20] investigating the predictive ability of the combination of transabdominal and peritoneal IUS for the middle- and long-term therapeutic efficacy of MTDs is an interesting future perspective. Finally, this was a single-center study, and the number of patients was limited. Although our study showed statistically significant findings, further prospective studies with larger cohorts will contribute to obtaining more robust insights into the longitudinal clinical significance of IUS monitoring in UC treatment. Notably, however, the single-

center design provided advantages in maintaining the quality of IUS procedures and the consistency of sonographic assessments. This is a crucial scientific strength of this study. Dissemination of an IUS training system is needed for future multicenter studies with standardized IUS protocols.

Conclusion

This study demonstrated that sonographic improvements 3 months after starting an MTD could predict SFCR and endoscopic healing with that MTD at 6 months.

Supplementary Materials

Material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.gastha.2024.04.007.

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Yoko Kimura, Jun Miyoshi, and Hiromu Morikubo conceived the study, designed the experiments, and prepared the manuscript. Yoko Kimura, Jun Miyoshi, Hiromu Morikubo, Haruka Komatsu, Chihiro Moue, and Hiromi Yonezawa collected and analyzed the data. Minoru Matsuura and Tadakazu Hisamatsu supervised the writing of the manuscript. Jun Miyoshi and Tadakazu Hisamatsu oversaw the entire project. All authors reviewed the manuscript.

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Ethical Statement:
This study was approved by the Institutional Ethics Committee of Kyorin University School of Medicine (Approval Number 2264) and conducted in accordance with the Declaration of Helsinki. This study used recorded data, and the ethics committee approved a waiver for informed consent.

Data Transparency Statement:
The data will be shared upon reasonable request to the corresponding author.

Reporting Guidelines:
Helsinki Declaration.