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Early resolution of bowel urgency by budesonide foam enema results in improved quality of life in patients with ulcerative colitis: a multicenter prospective observational study

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Background/Aims: Bowel urgency is an important symptom for quality of life determination in patients with ulcerative colitis (UC). Few clinical studies have focused on bowel urgency as an efficacy endpoint. Budesonide foam enema has shown efficacy for clinical and endoscopic improvement in mild-to-moderate UC. We evaluated the improvement of clinical symptoms (bowel urgency), safety, and treatment impact of twice-daily budesonide foam enema on the quality of life in patients with UC. **Methods:** This open-label, multicenter, prospective observational study comprised a 4-week observation period assessing the effectiveness and safety of twice-daily budesonide foam enema. Mild-to-moderate UC patients who had bowel urgency were included. Patients collected data daily in an electronic patient-reported outcome system or logbooks. The primary endpoint was the rate of resolution of bowel urgency at the end of the 4-week observation period. The rate of bowel incontinence was also assessed. **Results:** Sixty-one patients were enrolled. Of patients with a final evaluation, the rate of resolution of bowel urgency was 58.5% (31/53; 95% confidence interval, 44.1%–71.9%). Bowel urgency decreased over time, with a significant difference observed on day 7 versus day 0. Bowel incontinence showed a decreasing trend from day 5, with a significant difference confirmed on day 12 versus day 0. The clinical remission rate was 64.4% (38/59; 95% confidence interval, 50.9%–76.4%). One adverse event not related to budesonide rectal foam occurred. **Conclusions:** The findings suggest that bowel urgency can be improved early with twice-daily budesonide foam enema. No new safety signals were observed. **(Intest Res 2025;23:157-169)**

Key Words: Bowel urgency; Colitis, ulcerative; Quality of life

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown cause that affects the mucosa of the colon and rectum, with variable extension; it is characterized by frequent re-

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lapses and periods of remission.[1,2] Typical symptoms include chronic abdominal pain, diarrhea, bloody stools, tenesmus, weight loss, fever, and malaise.[2-4] Patients with distal lesions–even those with mild symptoms–may have severe mucosal damage and rectal function impairment (i.e., storing of stool, resulting in leakage and residual stool after defecation), which may reduce quality of life (QoL).[5,6]

Bowel urgency is thought to be a sign of disabling rectal continence due to inflammation in patients with UC. Bowel urgency–a sense of the sudden or immediate need to have a bowel movement–is among the most commonly reported and distressing symptoms.[3,7-10] Both bowel urgency and bowel incontinence are important triggers leading patients to seek medical attention. However, patients may find it difficult to discuss bowel urgency and may be hesitant to consult with their doctors regarding its symptoms. Furthermore, it has been noted that there is a gap in the perception of QoL between patients with UC and physicians.[10] Despite bowel urgency being an important symptom in the management of UC, few clinical studies have focused on the improvement or resolution of bowel urgency.

The goals of UC treatment are to control symptoms promptly and induce remission during the active phase, to maintain remission of the disease for as long as possible, and to improve QoL.[2,3,11] Treatment approaches for UC largely depend on the site and severity of the disease. Topical therapy with 5-aminosalicylic acid (5-ASA) or corticosteroids may be useful in treating rectal inflammation.[12] For proctitis, recent guidelines recommend mesalamine suppositories. Combinations of topical and oral 5-ASA can be used as the initial treatment for left-sided and extensive UC.[13,14]

Budesonide is a highly potent corticosteroid with a low systemic effect.[15] Its 2-mg rectal foam has been shown to be effective in reducing bloody stools and inducing clinical remission for mild-to-moderate UC.[1,16-21] Its long-term safety has also been shown.[22] Based on the efficacy of budesonide rectal foam on the rectal mucosa, we hypothesized that it might improve symptoms of bowel urgency and bowel incontinence in patients with UC and improve their QoL.

The objectives of this study were to evaluate the improvement of clinical symptoms (bowel urgency) and the impact of treatment with twice-daily budesonide foam enema among patients with UC, to investigate its efficacy in improving QoL per the Inflammatory Bowel Disease Questionnaire (IBDQ),[23,24] and to confirm its safety.

METHODS

1. Ethics

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Board of Kitasato Institute Hospital, Research Ethics Committee (No. 19057). The study was reviewed and approved by the ethical review boards of each participating institution (Supplementary Table 1). All patients provided written informed consent to participate in the study. This trial was registered with the UMIN Clinical Trials Registry, registration number UMIN000042027.

2. Study Design

This was an open-label, multicenter, prospective observational study conducted at 7 centers in Japan between October 2020 and May 2022. The study included a 4-week observation period, during which patients received remission induction therapy (Supplementary Fig. 1). This study observed the effectiveness of remission induction therapy with twice-daily budesonide foam enema as prescribed by the treating physicians for patients with UC who had bowel urgency. Patients were centrally registered and were allowed to withdraw from the study at any time.

3. Patients

Patients diagnosed with mild-to-moderate UC according to the diagnostic criteria of the Japanese Society of Gastroenterology[25] were eligible to participate. For inclusion, patients had to be aged ≥20 years with UC (any extent of disease) and to have answered sometimes, often, almost always, or always to the following question based on IBDQ (16 March 2018) Q11: "How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?", which assessed bowel urgency. Additionally, patients must have received a stable dose of oral 5-ASA in the 2 weeks before starting the observation period and have been deemed appropriate for treatment with twice-daily budesonide rectal foam (approved dosage and administration). Finally, patients had to be able to record treatment administration and clinical symptoms in an electronic patient-reported outcome (ePRO) system or a logbook and attend all required outpatient visits.

Patients were excluded from the study if any of the following applied within the indicated time prior to starting the observation period: received budesonide rectal foam (within 3 months), 5-ASA topical formulations (suppositories, enema formula-

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tions) (at the start), or corticosteroid enemas and corticosteroid suppositories (within 2 weeks) or had a dose change of immunomodulatory drugs (within 8 weeks). Patients were also excluded if they were being treated with systemic corticosteroids, Janus kinase inhibitors, or calcineurin inhibitors; cytapheresis; or currently or previously treated with biologics. Patients with a history of colorectal resection in the rectum and sigmoid colon or scheduled surgical treatment of the gastrointestinal tract during the study period, and those deemed inappropriate for study participation were excluded.

4. Data Collection

Collected data included the following patient background information: sex, age (date of birth), height, weight, smoking habit, and duration of illness. Data were also collected on whether patients were presenting with a first-onset or relapse of the active phase, the status of previous medications (within 8 weeks before the start of the observation period [week 0]), disease type, severity, site of active disease, and most recent administration of budesonide foam enema before the start of the observation period. The investigator determined the severity of the disease based on the diagnostic criteria of the Ministry of Health, Labour and Welfare.[25,26]

Patients were required to collect data daily and record it in an ePRO or a written logbook for the following items: the number of times budesonide foam enema was used, the number of times other drugs (oral formulations) were used, defecation presence and frequency (times/day), rectal bleeding status, assessment of bowel urgency, and evaluation of bowel incontinence. Patients recorded data in the ePRO or written logbooks from day 0. Day 0 before administration of the budesonide foam enema was used as baseline. Bowel urgency and bowel incontinence data were collected and evaluated according to IBDQ Q11 and Q26. The IBDQ scores were as follows: 1: always, 2: almost always, 3: often, 4: sometimes, 5: occasionally, 6: almost never, and 7: never.

For the QoL evaluation, the investigator applied the IBDQ at the beginning of observation (week 0) and at the end of observation (or at the time of discontinuation of observation). For clinical symptoms, the investigator recorded the following items at the beginning of observation (week 0) and at the end of observation (or at the time of discontinuation): the number of bowel movements per day before UC or at the time of the most improved UC signs and symptoms at the recent lesion (normal frequency; times/day); and partial Mayo score (stool frequency, rectal bleeding score, and physician's global assessment).

5. Study Endpoints

The primary endpoint was the rate of resolution of bowel urgency at the end of the 4-week observation period (percentage of patients who reported a bowel urgency score [IBDQ question 11] of 6 or 7 at the final evaluation).

The secondary endpoints were as follows: items related to bowel urgency, which included time to resolution of bowel urgency (time to when the bowel urgency score on defecation [IBDQ question 11] reached 6 or 7); items related to bowel incontinence, which included the rate of resolution of bowel incontinence (percentage of patients who reported a bowel incontinence score [IBDQ question 26] of 6 or 7 at the final evaluation), time to resolution of bowel incontinence (time to when the bowel incontinence score regarding defecation [IBDQ question 26] reached 6 or 7); changes in IBDQ scores and subscales, change in partial Mayo score, and clinical remission rate (clinical remission is defined as a blood stool score = 0 and defecation frequency score = 0 or a decrease of at least 1 point from 0 weeks using the partial Mayo subscore); time to resolution of defecation (time to when the stool frequency score reached 0); and time to resolution of blood stools (time to when the rectal bleeding score reached 0).

Safety was assessed by the occurrence of adverse events (AEs) and adverse drug reactions (ADRs) classed according to the Common Terminology Criteria for Adverse Events version 5.0, coded using the Medical Dictionary for Regulatory Activities, and tabulated by system organ class and preferred term.

6. Statistical Analysis

To avoid potential sources of bias, patients receiving budesonide rectal foam within the past 3 months were excluded. For the sample size calculations, it was assumed that the rate of resolution of bowel urgency and the rate of resolution of bowel incontinence were 30%, which is equivalent to the rate of complete mucosal healing based on the results of phase III clinical trials.[17] With a power of 90% and a significance level of 0.05, the number of cases required to demonstrate the rate of resolution of bowel urgency was 28 cases. From the survey of chief complaints in patients with UC,[10] approximately 60% of patients with a bowel urgency score of 1–4 (enrollment criteria for this study) have symptoms of bowel incontinence. However, because 30% of patients find it difficult to discuss bowel incontinence with their healthcare providers, we estimated that 67 cases (28 cases/0.6 [prevalence of bowel urgency score of 1-4]/0.7 [reporting rate of bowel incontinence]) were needed, assuming a 70% reporting rate of bowel incontinence symp-

toms in this study. Furthermore, if approximately 20% of patients would drop out because of medication noncompliance and other reasons, the target sample size was 80 cases.

The analytical populations were the full analysis set comprising all eligible patients, the medication compliance population comprising all eligible patients with a compliance of ≥50%, the population of patients who completed the study, and the safety analysis population.

Regarding the statistical measures used, number of cases, mean (standard deviation), median, quartiles (interquartile range) and range (minimum value–maximum value) were calculated for continuous variables, and frequencies and percentages for categorical data. The rate of resolution (or the primary endpoint) and its 95% confidence interval (CI) were calculated.

Secondary endpoints were evaluated according to the analysis plan. Significance was defined as $P<0.05$. The number of patients in clinical remission at the last evaluation, the clinical remission rate and the 95% CI (based on the Clopper-Pearson method) were calculated. Stool frequency score and a rectal bleeding score of ≥1 at the final evaluation were defined as non-normalization. Other stratified analyses, such as by disease type and exploration of factors affecting the primary evaluation, were also conducted. For safety, the frequency and incidence of AEs and ADRs were calculated for patients who received budesonide rectal foam at least once. Missing data were not imputed. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

RESULTS

1. Patient Characteristics

Of the 62 registered patients with active UC and bowel-urgency symptoms, 61 were enrolled, 58 completed the study, and 3 discontinued the study. Five patients were excluded from the analysis at the final evaluation because they did not submit the IBDQ. The reasons for discontinuation were withdrawal of consent (n=2) and AEs (n=1). Overall, 53 patients had a final evaluation (Fig. 1). Although the enrollment goal of 80 patients was not achieved, the enrollment period was not extended because the total number of patients enrolled was close to the minimum required sample size of 67. Fifty-two patients (85.2%) had a medication compliance rate of ≥50%.

Table 1 summarizes the main background characteristics of patients. In total, 52.5% of patients were female, the median (interquartile range) age was 41.0 (30.0–54.0) years, and 91.8% of patients had no smoking habit. Nearly 60% (57.4%) had UC for more than 5 years, and 72.1% had moderate disease severity. The extent of the disease was most commonly pancolitis (28 patients, 45.9%), followed by left-sided colitis (26 patients, 42.6%). Forty-six patients (75.4%) had no prior history of budesonide rectal foam use.

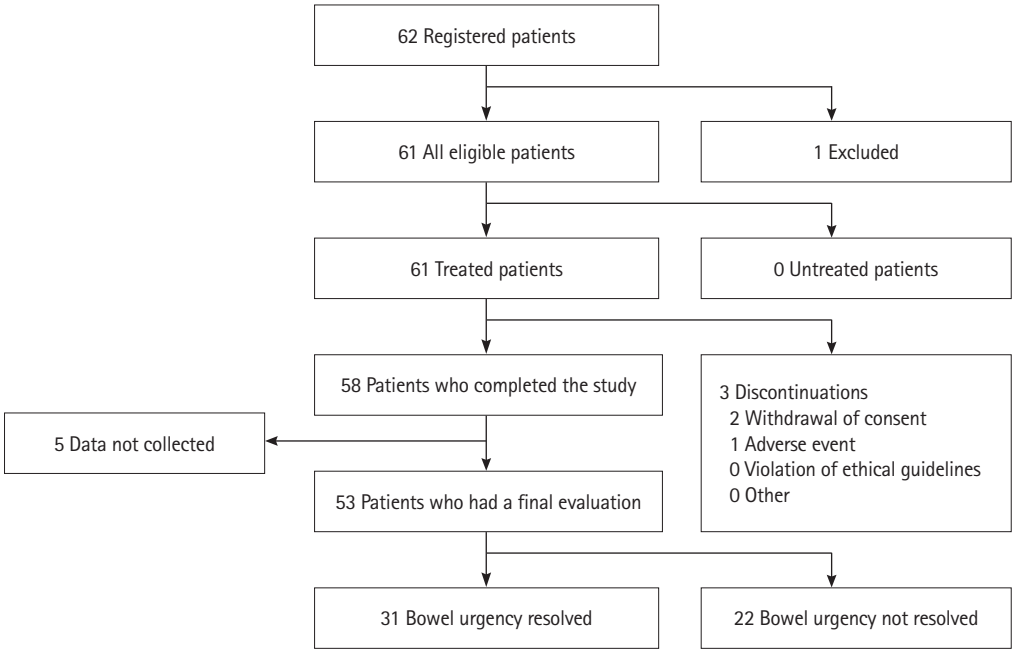

Fig. 1. Patient disposition throughout the study.

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Table 1. Patient Background Characteristics

Characteristic	Value (n = 61)
Sex	
Male	29 (47.5)
Female	32 (52.5)
Age (yr)	41.0 (30.0–54.0)
Height (cm)	165.0 (158.5–172.0)
Body weight (kg)	59.0 (51.0–67.0)
Partial Mayo score	5.0 (4.0–6.0)
Smoking habit	
No	56 (91.8)
Yes	5 (8.2)
Duration of illness	
< 12 wk	3 (4.9)
12 wk to < 1 yr	8 (13.1)
1 to < 5 yr	15 (24.6)
≥ 5 yr	35 (57.4)
First-onset and relapse in the active phase	
Initial	6 (9.8)
Relapse	55 (90.2)
Previous medications (within 8 wk before the start of observation)	
5-ASA rectal formulation	
No	52 (85.2)
Yes	9 (14.8)
5-ASA suppository formulation	
No	57 (93.4)
Yes	4 (6.6)
5-ASA oral formulation	
No	5 (8.2)
< 3,600 mg/day	10 (16.4)
3,600 to < 4,800 mg/day	17 (27.9)
4,800 mg/day	29 (47.5)
Immunomodulator	
No	56 (91.8)
Yes	5 (8.2)
Disease pattern	
Proctitis	7 (11.5)
Left-sided colitis	26 (42.6)
Pancolitis	28 (45.9)
Disease severity	
Mild	17 (27.9)
Moderate	44 (72.1)
Severe	0
Active lesion site[a]	
Rectum only	11 (18.0)
Up to the sigmoid colon	25 (41.0)
Up to the descending colon	6 (9.8)
From the descending colon to the mouth	10 (16.4)
Unknown	9 (14.8)
No. of defecations per day (normal frequency)	1.5 (1.0–2.0)
History of administration of budesonide rectal foam	
No	46 (75.4)
Yes	15 (24.6)

Values are presented as number (%) or median (interquartile range).
[a]Indicates the extent of inflammation assessed during colonoscopies performed within the year prior to the start of the study.
5-ASA, 5-aminosalicylic acid.

2. Primary Endpoints

The rate of resolution of bowel urgency was 50.8% (31/61; 95% CI, 37.7%–63.9%). For patients who had a final evaluation, the rate of resolution of bowel urgency was 58.5% (31/53; 95% CI, 44.1%–71.9%).

3. Secondary Endpoints

There were no significant differences in the rate of bowel urgency resolution according to disease type, with rates of 53.6% (15/28; 95% CI, 33.9%–72.5%) for pancolitis and 48.5% (16/33; 95% CI, 30.8%–66.5%) for the other types ($P = 0.80$). There were also no significant differences in the rates of resolution of bowel urgency with or without budesonide rectal foam use (46.7% [7/15; 95% CI, 21.3%–73.4%] and 52.2% [24/46; 95% CI, 36.9%–67.1%]), respectively ($P = 0.77$).

On day 0, the bowel urgency rate was 85.7% (18/21), which decreased to 47.2% (25/53) on day 7, and to 25.0% (3/12) on day 30 of budesonide foam treatment (Fig. 2A). Time to resolution of bowel urgency was estimated at 7 days after initiating budesonide foam treatment. Bowel urgency decreased over time, with a significant difference observed on day 7 compared with day 0 ($P < 0.05$).

At baseline, 25 out of 61 patients (41.0%) had bowel incontinence. Bowel incontinence showed a decreasing trend from day 5, and a significant difference was confirmed on day 12 compared with day 0 ($P < 0.05$) (Fig. 2B). From day 26 onwards, no patients reported fecal incontinence. The rate of resolution of bowel incontinence at the time of the final evalua-

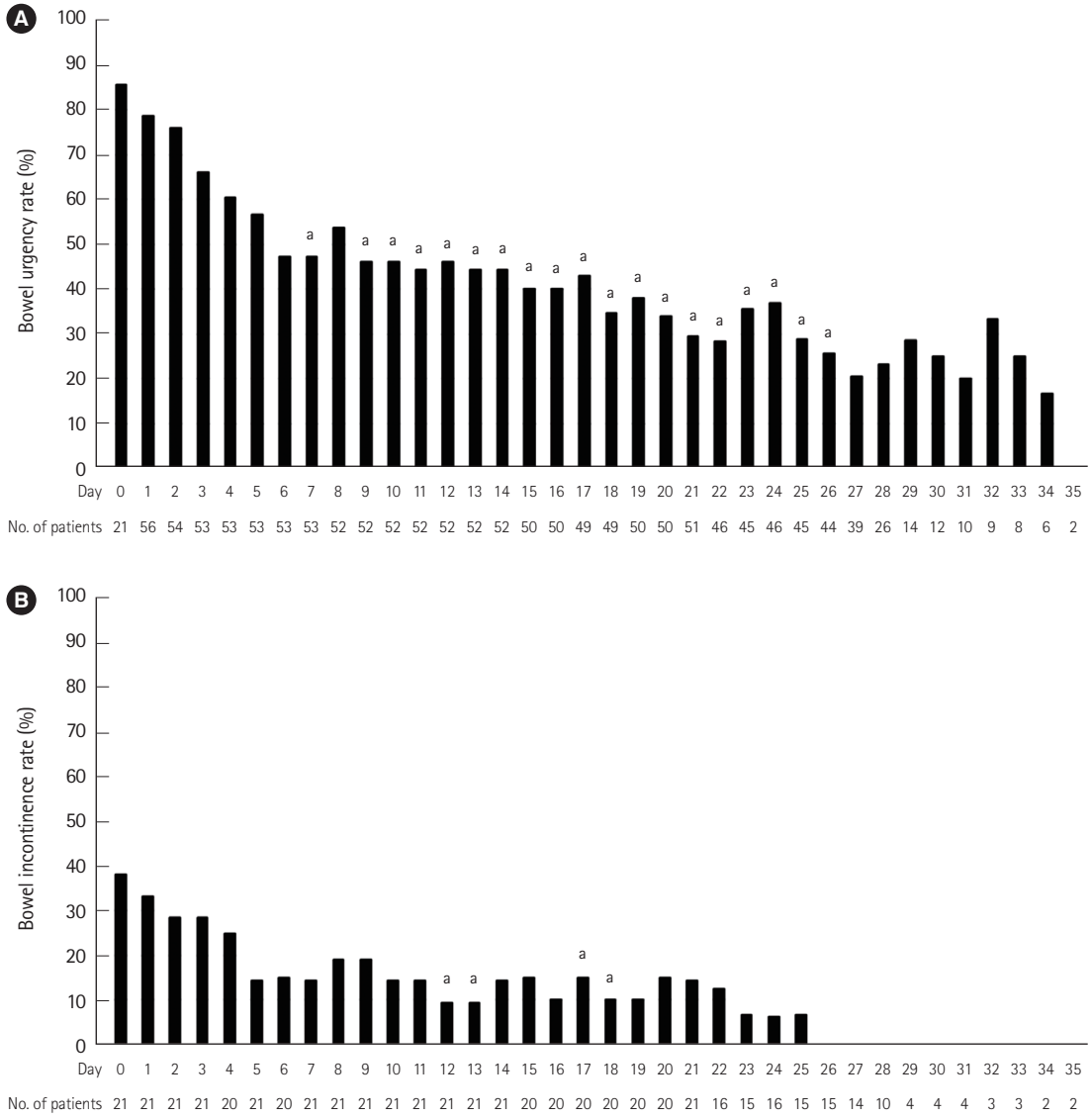

Fig. 2. Proportion of patients experiencing (A) bowel urgency and (B) bowel incontinence, and without normalization of (C) stool frequency or (D) rectal bleeding throughout the study. (A, B) The vertical axis indicates the percentages of patients with bowel urgency and bowel incontinence scores of 1–5, respectively. (C, D) The vertical axis shows the percentages of patients with stool frequency and rectal bleeding subscores of 1–3, respectively. Day 0 is before the start of treatment, and day 1 and subsequent days are the number of days since the start of budesonide foam enema treatment. [a]$P<0.05$ (compared with Day 0 by McNemar test). *(Continued to the next page)*

tion was 72.0% (18/25; 95% CI, 50.6%–87.9%).

Of the 61 patients with bowel urgency, 14 out of 25 patients (56.0%) who responded as having bowel incontinence on the IBDQ before administration had both bowel incontinence and bowel urgency resolved at the end of the observation period. Nevertheless, 4 patients still had bowel urgency despite the resolution of bowel incontinence.

The changes in IBDQ scores and subscales are shown in Table 2. Overall, the median (interquartile range) IBDQ total score at baseline was 141.0 (121.0–161.0), which increased to 181.0 (160.0–197.0) at the final evaluation, with a median change in the score (from baseline) at the final evaluation of +29.0 points ($P<0.001$). Improvements were observed for all dimensions, but changes were more marked for bowel symptoms (+1.3).

Among patients whose bowel urgency resolved, the median change in IBDQ total score (from baseline) at the final evaluation was +43.0 points, which represented a significant increase in the score ($P=0.006$). All IBDQ subscale scores except social function increased significantly from baseline at the final eval-

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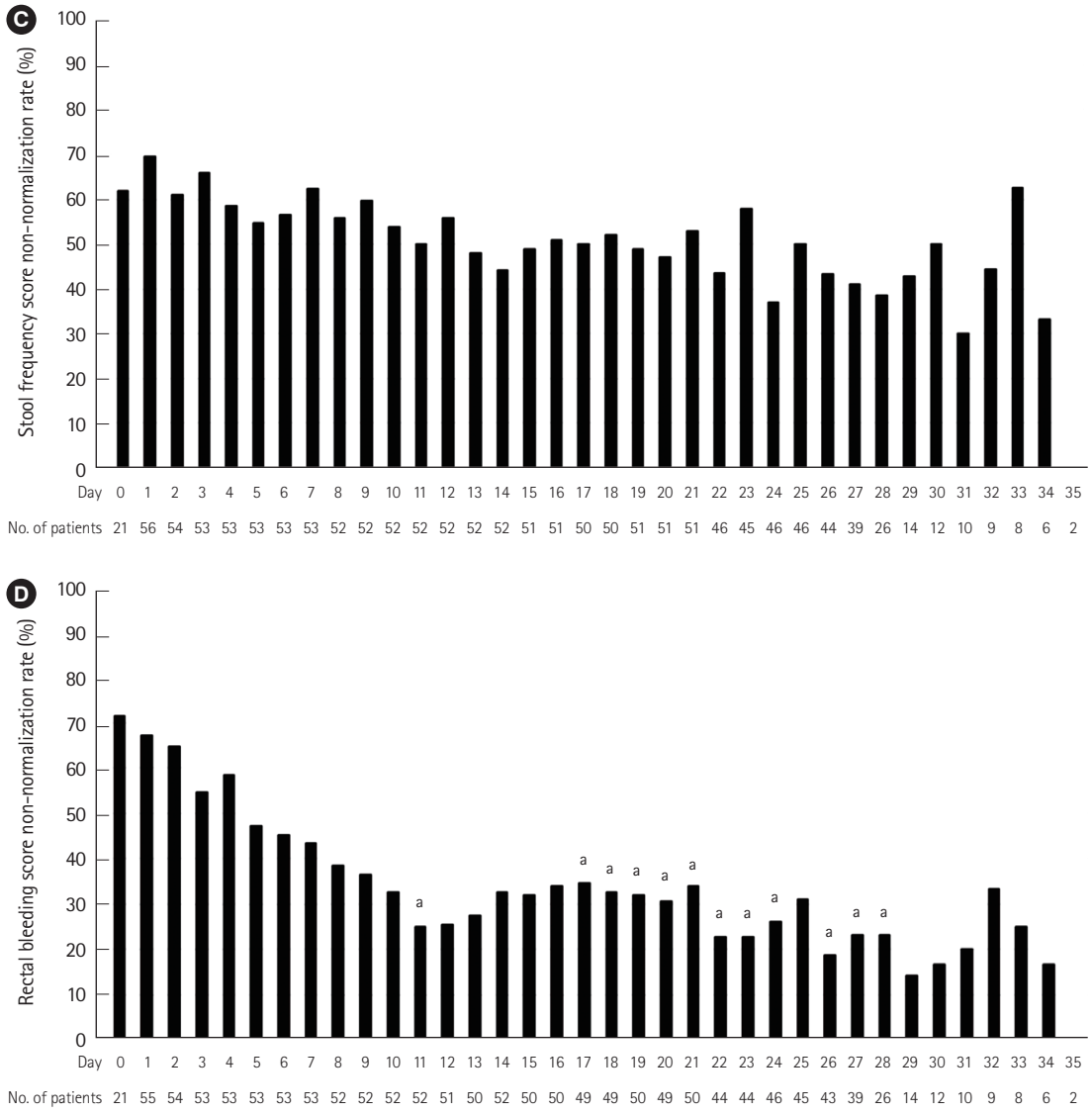

Fig. 2. Continued.

Table 2. Changes in Quality of Life per Changes in IBDQ Total Score and Subscale (n = 61)

	IBDQ total score	IBDQ subscale score			
		Bowel symptoms	Emotional function	Systemic symptoms	Social function
Baseline (n = 59)	141.0 (121.0–161.0)	4.3 (3.5–5.1)	4.8 (4.0–5.4)	4.0 (3.4–4.6)	5.0 (3.6–6.0)
Final (n = 53)	181.0 (160.0–197.0)	5.9 (5.2–6.2)	5.6 (4.9–6.1)	5.2 (4.6–5.8)	5.8 (5.4–6.8)
Change (n = 53)	29.0 (13.0–55.0)[a]	1.3 (0.4–2.2)	0.8 (0.3–1.3)	0.8 (0.2–1.8)	0.8 (0.4–1.8)

Values are presented as median (interquartile range).
[a] $P < 0.001$ (Wilcoxon test).
IBDQ, Inflammatory Bowel Disease Questionnaire.

uation (Table 3). In contrast, there was no significant increase in the IBDQ total score or any of the IBDQ subscale scores among patients whose bowel urgency did not resolve. A comparison of patient background characteristics in patients whose bowel urgency did or did not resolve showed no significant differences between the 2 groups except for the distribution of disease patterns (proctitis, left-sided colitis, and pancolitis) (Supplementary Table 2).

Table 3. Changes in Quality of Life per Changes in IBDQ Total Score and Subscale by Whether Bowel Urgency Resolved (n = 53)

	IBDQ total score	IBDQ subscale score			
		Bowel symptoms	Emotional function	Systemic symptoms	Social function
Bowel urgency not resolved (n = 22)					
Baseline	135.5 (121.0–168.0)	4.2 (3.4–5.3)	4.7 (4.0–5.1)	4.0 (3.6–4.6)	4.4 (3.2–6.0)
Final	159.0 (146.0–179.0)	5.2 (4.6–5.7)	4.9 (4.3–5.8)	4.6 (3.8–5.2)	5.4 (4.8–5.8)
Change	15.0 (4.0–43.0)	0.7 (0.1–2.0)	0.3 (–0.1–0.8)	0.4 (0.0–1.0)	0.7 (0.0–1.4)
Bowel urgency resolved (n = 31)					
Baseline	154.0 (136.0–161.0)	4.4 (4.1–5.1)	4.8 (4.3–5.4)	4.2 (3.4–4.8)	5.4 (4.2–6.0)
Final	189.0 (178.0–203.0)	6.2 (5.8–6.6)	6.0 (5.4–6.4)	5.2 (5.0–6.2)	6.6 (5.8–7.0)
Change	43.0 (22.0–62.0)	1.4 (1.0–2.3)	1.2 (0.6–1.5)	1.2 (0.6–2.0)	1.0 (0.4–2.0)
P-value[a]	0.006	0.026	0.001	0.006	0.274

Values are presented as median (interquartile range).
[a]Wilcoxon test.
IBDQ, Inflammatory Bowel Disease Questionnaire.

Table 4. Summary of Bowel Urgency Scores by Clinical Remission Status

Urgency measure	No clinical remission (n = 18)	Clinical remission (n = 35)	*P*-value
IBDQ question 11 score, No. (%)			
1	2 (11.1)	0 (0.0)	
2	1 (5.6)	2 (5.7)	
3	1 (5.6)	2 (5.7)	
4	3 (16.7)	1 (2.9)	
5	3 (16.7)	7 (20.0)	
6	6 (33.3)	17 (48.6)	
7	2 (11.1)	6 (17.1)	
Mean ± SD	4.7 ± 1.9	5.5 ± 1.3	
Median (IQR)	5.0 (4.0–6.0)	6.0 (5.0–6.0)	0.096[a]
Bowel urgency status, No. (%)			0.150[b]
Presence (score 1–5)	10 (55.6)	12 (34.3)	
Absence (score 6 or 7)	8 (44.4)	23 (65.7)	

[a]Wilcoxon rank-sum test.
[b]Fisher exact test.
IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation; IQR, interquartile range.

Proportions of the partial Mayo scores for stool frequency are shown in Fig. 2C. Stool frequency scores varied throughout the observation period and tended to decrease. On day 31, patients reported the most marked changes in the stool frequency scores. No significant difference was observed.

The proportions of the partial Mayo scores for rectal bleeding are shown in Fig. 2D. In contrast to the observations related to stool frequency, the rectal bleeding score decreased over time, with a significant reduction observed on day 11 compared with day 0 ($P < 0.05$).

The clinical remission rate was 64.4% (38/59; 95% CI, 50.9%–76.4%). Of the 18 patients who did not achieve clinical remission, 8 (44.4%) had improvements in bowel urgency (Table 4), and of the 35 patients who did achieve clinical remission, 12 (34.3%) still had bowel urgency. No statistically significant difference was found between the clinical remission group and the non-clinical remission group regarding the disappearance of bowel urgency ($P = 0.150$). There was also no significant difference in the median urgency score between the 2 groups ($P = 0.096$).

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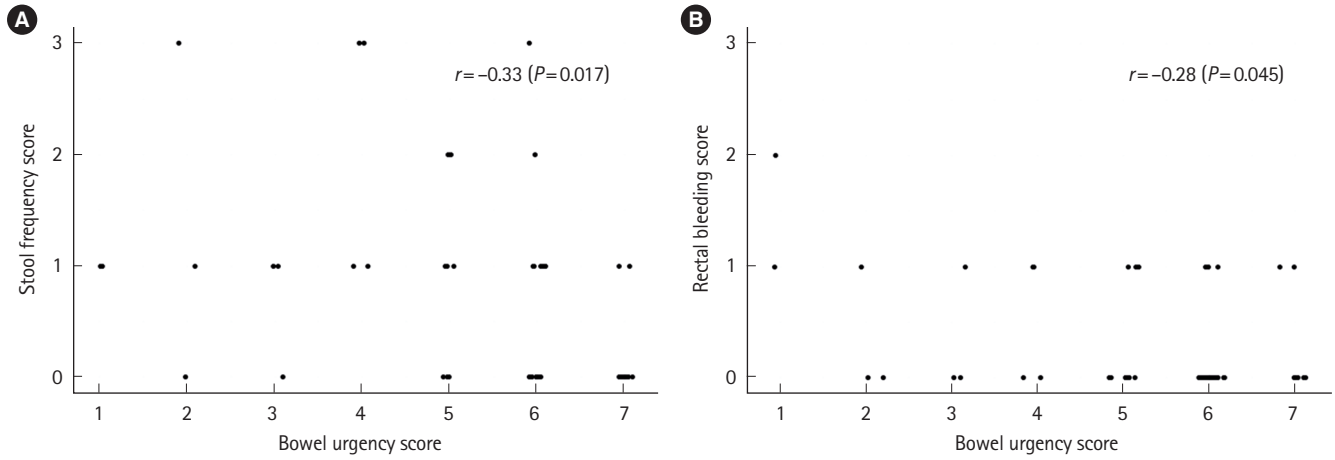

Fig. 3. Association between bowel urgency scores (IBDQ question 11) and stool frequency (A) and rectal bleeding (B) scores at the final evaluation. IBDQ, Inflammatory Bowel Disease Questionnaire; *r*, Spearman's rank correlation coefficient.

Bowel urgency showed weak correlations with stool frequency (Fig. 3A) and rectal bleeding (Fig. 3B) (a lower bowel urgency score indicates more severe bowel urgency), with Spearman rank correlation coefficients of $r=-0.33$ ($P=0.017$) and $r=-0.28$ ($P=0.045$), respectively. Bowel urgency also correlated with physician's global assessments and partial Mayo scores, with Spearman rank correlation coefficient values of $r=-0.48$ ($P<0.001$) and $r=-0.43$ ($P=0.001$), respectively (data not shown).

AEs and ADRs were evaluated. Only one AE occurred, which was a case of worsening UC (1.6%, 1/61). No ADRs were observed.

DISCUSSION

Few clinical studies have focused on the improvement/resolution of bowel urgency among patients with UC. This study of bowel urgency and bowel incontinence using daily recordings of IBDQ questions by patients undergoing UC treatment with budesonide rectal foam enema revealed that bowel urgency decreased by 50.8%, with improvement in bowel urgency on day 7. Budesonide foam enema led to the resolution of bowel urgency in nearly 60% of patients and the resolution of bowel incontinence in over 70%. Furthermore, numerical improvements in IBDQ total and bowel symptom scores suggest that budesonide foam enema contributed to improving QoL. In this study, treatment with twice-daily budesonide foam enema was considered safe as no ADRs, and only 1 AE (1.6%), were reported.

The clinical remission rate in the phase III placebo-controlled trial of budesonide 2-mg rectal foam in patients with mild-to-moderate UC was 40.6%,[17] whereas it was 64.4% in the current study. In contrast to the phase III trial,[17] in which all cases were naïve to budesonide foam enema, 24.6% had a prior history of its use in the present study. This may explain why the remission rate was high.

The incidence of AEs was substantially lower in this study compared with that of the phase III trial, and no ADRs were observed.[17] The incidence of ADRs in the phase III trial was 17.2% at week 6 and 5.0% from week 6 to week 12, and that of AEs was 45.3% at week 6 of treatment and 30.0% from week 6 to week 12[17]; none of the AEs were unexpected. The shorter observation period in the present study (4 weeks) compared with the phase III trial (12 weeks) might be an explanation for the observed difference in safety findings between the studies.[17]

It has been reported that half of patients with UC have inflammation limited to the distal colon (proctitis or proctosigmoiditis) that primarily causes urgency.[27] We believe budesonide rectal foam targets inflammation in the distal colon and rectum. In fact, there were no differences in the background characteristics between patients who did or did not have their bowel urgency resolved. Similar to our study, other rectal enemas have also been reported to contribute to the resolution of bowel urgency.[27] A report of improvement in bowel urgency with a rectal formulation of 5-ASA 2 g plus L-1 butyrate 80 mL twice daily for 6 weeks in patients with mild-to-moderate UC showed an improvement ($P<0.05$) in bowel urgency and bowel incontinence.[28] Conversely, the group receiving 5-ASA 2 g plus 80 mL saline twice daily did not particularly show improvements in bowel urgency.[28] UC may also lead to changes in smooth

muscle tone, sensitization within the wall, and increased contractile response of the rectum, as well as the development of submucosal fibrosis.[29-31] Some patients achieved clinical remission but still had bowel urgency, which remained despite the resolution of bowel incontinence. In addition, although the correlation was weak, some patients' bowel urgency did not resolve, even when their stool frequency score or rectal bleeding score improved to 0. This aligns with a Japanese internet survey that investigated the symptoms, impact, and treatment of UC, and communication between patients and medical professionals, in which there was still a relatively high incidence of bowel urgency, even in participants with stool frequency and rectal bleeding scores of 0.[10] This suggests that underlying pathological conditions other than inflammation may be present.

A report examining the clinical value of QoL indicates that an improvement in IBDQ total scores of >20 points is clinically significant.[32] The median change in the IBDQ score measured in this study was +29 points in total. Additionally, IBDQ total score increased significantly in patients whose bowel urgency resolved but not in those whose bowel urgency did not resolve, indicating that bowel urgency affects QoL. Our findings suggest that budesonide foam enema therapy resulted in a clinically significant improvement in QoL. This is relevant, as a recent online survey confirmed that bowel symptoms–specifically bowel urgency and bowel incontinence–were among the most burdensome and correlated with decreased QoL.[10] Furthermore, patients mentioned that, while they wanted these symptoms to improve, they were embarrassed to discuss them with their healthcare providers and seek treatment.[10] Thus, physicians must be mindful of communicating with patients about bowel urgency and bowel incontinence, which can negatively impact daily life, and openly discuss safe and effective treatment alternatives to ensure symptom management and improve patient QoL.

The relevance of the results of this study to clinical practice is that patients' bowel urgency can be improved early during treatment with budesonide rectal foam; thus, the use of budesonide rectal foam is useful for improving bowel urgency in patients with mild-to-moderate UC during the remission induction period. Furthermore, the effects of budesonide rectal foam can be expected regardless of disease type and whether or not budesonide rectal foam is used.

The main limitations of this study were the single-arm, before-and-after comparative design and small sample sizes, 61 patients were enrolled against a target of 80 cases. As colonoscopies were not performed as part of this study, the extent of inflammation could only be assessed on the basis of colonoscopies performed within the year prior to the start of the study. Additionally, data on biomarkers[33] were not collected because we focused on patient-reported outcomes such as bowel urgency. Data collected in the logbooks were collected according to the IBDQ questionnaire and were not validated. Many patients started entering data on day 1 (the first day of budesonide use) but not on day 0 (the day before); therefore, the "true" baseline data on bowel urgency were not accurately collected for some patients.

In conclusion, budesonide foam enema is effective for bowel urgency as assessed by IBDQ Q11 and helps improve QoL in patients with UC.

ADDITIONAL INFORMATION

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Conflict of Interest

Kobayashi T reports personal fees from AbbVie GK, Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Mitsubishi-Tanabe Pharma Corporation, Pfizer Japan Inc.; research grants from AbbVie GK, Activaid, Alfresa Pharma Corporation, JMDC Inc., Gilead Sciences Inc., Nippon Kayaku Co., Ltd., Eli Lilly Japan K.K., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Google Asia Pacific Pte, Ltd.; scholarship grants from Mitsubishi-Tanabe Pharma Corporation, Zeria Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., EA Pharma Co., Ltd.; endowed chair from JIMRO Co., Ltd., Zeria Pharmaceutical Co., Ltd., Alfresa Pharma Corporation, Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co., outside the submitted work. Fujii T reports personal fees from AbbVie GK, Janssen Pharmaceutical K.K.; research grants from AbbVie GK, Alfresa Pharma Corporation, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, EA Pharma Co. Ltd., Eisai Co. Ltd., Gilead Sciences, Janssen Pharmaceutical K.K., Kissei Pharmaceutical Co., Ltd., Eli Lilly and Company, Mebix Inc., Sanofi K.K., Takeda Pharmaceutical Co., Ltd., outside the submitted work. Shinzaki S reports personal fees from EA Pharma Co., Ltd., outside the submitted work. Yamada A reports research grants from AbbVie GK, Mitsubishi-Tanabe

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Data Availability Statement

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

Author Contributions

Concept and design of the study: Kobayashi T, Hibi T, Bamba S, Shinzaki S, Moriya K, Fujii T, Yamada A, Inagaki K, Iwayama K. Conduct of the study: Kobayashi T, Hibi T, Bamba S, Shinzaki S, Moriya K, Fujii T, Yamada A, Hisabe T, Sagami S, Amano T, Hibiya S, Takatsu N. Interpretation of data: Kobayashi T, Hibi T, Bamba S, Shinzaki S, Moriya K, Fujii T, Yamada A, Hisabe T. Drafting of the manuscript: Kobayashi T, Inagaki K, Iwayama K. Manuscript review and editing: Kobayashi T, Hibi T, Bamba S, Shinzaki S, Moriya K, Fujii T, Yamada A. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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