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Clinical Background Factors as Predictors of the Efficacy of 5-Aminosalicylic Acid Suppositories in Patients with Ulcerative Colitis

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Keywords
Ulcerative colitis · 5-ASA suppository · Clinical background · Lichtiger Colitis Activity Index · Ulcerative Colitis Endoscopic Index of Severity

Abstract

Introduction: Although the efficacy of 5-aminosalicylic acid (ASA) suppositories for ulcerative colitis (UC) has been reported in many studies, many studies have also described poor adherence to 5-ASA suppository regimens. We aimed to identify the clinical background factors that influence adherence to 5-ASA suppositories to improve adherence and efficacy of the treatment. ***Methods:*** We conducted a retrospective cohort study of 61 patients with active UC who were using 5-ASA suppositories. All patients underwent endoscopy and rectal biopsy for histological diagnosis prior to 5-ASA suppository treatment. The efficacy of 5-ASA suppository treatment was compared in relation to clinical background factors (sex, age, disease duration, disease type, clinical activity, Ulcerative Colitis Endoscopic Index of Severity, histological activity, serum C-reactive protein level, concomitant use of immunomodulators, history of steroid use, and dose of oral 5-ASA). ***Results:*** The efficacy of 5-ASA suppositories was significantly related to low Lichtiger Colitis Activity Index (LCAI) scores and proctitis type prior to its use. In terms of sex, females tended to show higher efficacy. Multivariate logistic regression analysis using these three factors showed high predictive value for the efficacy of 5-ASA suppositories (AUC, 0.788; sensitivity, 87.2%; and specificity, 63.7%). ***Conclusion:*** This study is the first to extract clinical background factors for predicting the efficacy of 5-ASA suppositories. The use of 5-ASA suppositories in patients who are expected to show efficacy will be effective in improving patient co-operation.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology that is characterized by inflammation of the colonic mucosa. It has been reported that rectal involvement is observed in 95% of UC cases [1–3]. The treatment of UC is based on the severity and extent of the disease [4]. For more distal disease, rectally administered topical agents can be used to deliver drugs directly to the site of inflammation in the distal colon, reducing the need for systemic drug administration [4, 5]. In the "Third European Evidence-Based Consensus on the Diagnosis and Management of Ulcerative Colitis, Part 2: Current Management," published in 2017, topical mesalazine is superior to topical steroids and oral mesalazine to the patients with proctitis type because suppositories, in particular, have the potential to effectively deliver the drug to the rectum [6].

Topical application of mesalazine as a suppository has been reported to be more effective than oral treatment in patients with proctitis or left-sided colitis [7, 8]. The first placebo-controlled trial for the use of 5-aminosalicylic acid (5-ASA) suppositories in UC was performed in 1965 [9]. The effect of rectal administration of 5-ASA suppositories has been reported to be superior to that of rectal steroids [10–12]. The combination of oral and rectal mesalazine administration has also been reported to be effective [13]. A Cochrane review in 2010 highlighted the predominant effectiveness of rectal mesalazine treatment, which manifested as clinical, endoscopic, and histological improvements with an odds ratio of 6–8 in comparison with the placebo [14]. Subsequently, various clinical studies have reported the usefulness of topical mesalazine formulations for distal UC. Randomized controlled trials have shown that the clinical and endoscopic efficacy of topical mesalazine for distal UC was approximately 80% [15]. However, adherence to topical therapy, including 5-ASA suppositories, 5-ASA enema, and rectal steroids, has been reported to be low. A prospective cohort study demonstrated that 55% of patients self-reported occasional nonadherence, and 71% of patients were non-adherent to their prescribed regimen [16]. The reasons for nonadherence to topical therapy were poor acceptance of the transanal method of administration and the busy lifestyles of the patients [4]. In practice, adherence was significantly lower with topical therapy than with oral therapy [17].

If the efficacy of 5-ASA suppository treatment could be predicted in advance on the basis of clinical background factors, it may be possible to improve treatment adherence by encouraging patients who were predicted to show high efficacy to become aware of their use and by encouraging physicians to prescribe these regimens with confidence in their efficacy. However, no study to date has been attempted to predict the efficacy of 5-ASA suppositories on the basis of clinical background factors before treatment. Therefore, this study aimed to improve adherence and therapeutic efficacy of 5-ASA suppositories by evaluating the clinical course of UC patients treated with 5-ASA suppositories retrospectively elucidating the clinical factors that influence the efficacy of 5-ASA suppositories.

Methods

Study Design and Participants

A retrospective observational cohort study was conducted with a total of 61 UC patients who received treatment with a 5-ASA suppository between July 2013 and November 2020. All participants underwent colonoscopy for evaluation and histological examination of the rectum immediately prior to the initiation of 5-ASA suppository treatment. In the present study, the site of exacerbation in all cases was limited to the anal site from Rs. All patients attended the gastroenterology outpatient clinic at the hospital of our university. After the initiation of 5-ASA suppository treatment, no other treatment was added, and the clinical activity was evaluated 4–8 weeks after the start of 5-ASA suppository treatment. Patients who had received any form of intensified therapy within 2 weeks prior to initiation of 5-ASA suppositories were excluded. For thiopurine, patients who had started within the previous 4 weeks were also excluded.

Diagnostic Evaluation

Three endoscopists who were blinded to the patient details and clinical data evaluated all of the endoscopic images. Among them, two were expert endoscopists (experts A and B) who had previously performed >10,000 conventional colonoscopies, while the third was a non-expert (non-expert C) who had previously performed <2,000 conventional colonoscopies. This analysis was performed on the basis of a previous report [18].

Assessment of Disease Activity

Clinical disease activity was determined using the Lichtiger Colitis Activity Index (LCAI) [19]. Clinical remission was defined as a score of 4 or less on the LCAI, and active phase was defined by a score of 5 or more. Treatment efficacy is defined as an improvement to an LCAI score of 4 or less.

Histopathological Assessment

Inflammation in the biopsy specimen was evaluated on the basis of the Geboes score [20] by an expert pathologist. Biopsy specimens were collected from endoscopically active sites in the rectum, and active histological inflammation was defined by a Geboes score of ≥2 B.1.

Table 1. Patient characteristics and background factors

Total number	61
Sex (female/male)	32/29
Age, years	46.9±18.4
Disease duration, months	112.5±112.0
Smoking history, *n* (%)	6 (9.8)
Disease location, *n* (%)	
Extensive	29 (47.5)
Left-sided	14 (23.0)
Rectum	18 (29.5)
Current medication, *n* (%)	
Oral 5-aminosalicylates	58 (95.1)
Prednisolone	0 (0.0)
Azathioprine	15 (24.6)
Biologics	
IFX	1 (1.6)
GLM	1 (1.6)
VED	1 (1.6)
Lichtiger Colitis Activity Index	6.62±1.54
Serum C-reactive protein level	0.20±0.43
Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (2:3:4)	23:29:9
History of oral steroid, *n* (%)	24 (39.3)

Statistical Analysis

Analysis of variance was performed to assess the trend of the mean, stratified according to the normally distributed continuous variables. The trend test was based on linear contrast. All analyses were performed with JMP PRO version 14.0.0 (SAS Institute Japan Ltd). Continuous data were described as mean ± standard deviation, if normally distributed, or median and interquartile range (25%, 75%), if not normally distributed.

Results

Patient Baseline Demographic Variables

The characteristics of the 61 patients included in this study are listed in Table 1. Among the 61 patients, 39 (63.9%) showed an LCAI improvement to a score of 4 or less after 4–8 weeks of treatment, and 22 patients (36.1%) showed active disease with an LCAI score of 5 or more.

Clinical Background Factors Influencing the Effectiveness of 5-ASA Suppositories

Figure 1 shows the relationship between the effectiveness of 5-ASA suppositories and clinical background factors. The LCAI score before treatment was significantly lower in cases that subsequently showed clinical effectiveness ($p = 0.0127$). In terms of disease type, the proportion of proctitis type was significantly higher in cases that showed effectiveness of 5-ASA suppositories ($p = 0.0412$). Despite the absence of significant sex-related differences, the results showed a trend toward a higher percentage of effectiveness among female patients ($p = 0.0587$). No statistically significant differences were found in other clinical characteristics such as age ($p = 0.6359$), disease duration ($p = 0.9436$), endoscopic findings (Ulcerative Colitis Endoscopic Index of Severity) (2 vs. 3 [$p = 0.6957$], 3 vs. 4 [$p = 0.1828$], 2 vs. 4 [$p = 0.1146$]), histological activity ($p = 0.6539$), serum CRP level ($p = 0.3447$), history of steroid use ($p = 0.4631$), concomitant immunomodulators ($p = 0.8393$), and dose of oral 5-ASA ($p = 0.1331$). The efficacy rates of 5-ASA suppositories by the type of oral 5-ASA preparation at the time of the initiation of 5-ASA suppositories were 62.1% (18/29) for pH-dependent, 63.2% (12/19) for time-dependent, 60.0% (6/10) for MMX coated, and 100% (3/3) for no 5-ASA. There were no significant differences between those groups. In the multivariate analysis performed with LCAI, disease type, and sex, only LCAI was extracted as a factor influencing the effectiveness of the 5-ASA suppository (Table 2).

Efficacy in Each Item of the LCAI

Because disease activity prior to 5-ASA suppository administration was found to influence subsequent efficacy, efficacy in each item of the LCAIs was further examined. Figure 2a shows the effect of defecation frequency score, and 2b shows the effect of blood stool score. Abdominal pain score showed no correlation with efficacy. Each score decreased in effectiveness as the score increased, but the trend was more pronounced for the defecation frequency score. Abdominal pain score showed no correlation with efficacy (Fig. 2c).

Validation of Diagnostic Performance

Sensitivity, specificity, and AUC values of LCAI in predicting the effectiveness of 5-ASA suppositories were calculated. As shown in Figure 3a, when the cutoff value was 7.0, the sensitivity, specificity, and AUC for prediction of effectiveness using LCAI alone were 87.2%, 54.5%, and 0.70746, respectively. A multivariate model based on logistic regression analysis including LCAI, disease type, and sex showed better performance in predicting the effectiveness of 5-ASA suppositories, with sensitivity, specificity, and AUC of 87.2%, 63.7%, and 0.78846, respectively (Fig. 3b).

Discussion

In the present study, we investigated the clinical background factors that could serve as predictors of the effectiveness of 5-ASA suppositories in UC patients. We found that the disease activity (LCAI) at the time of

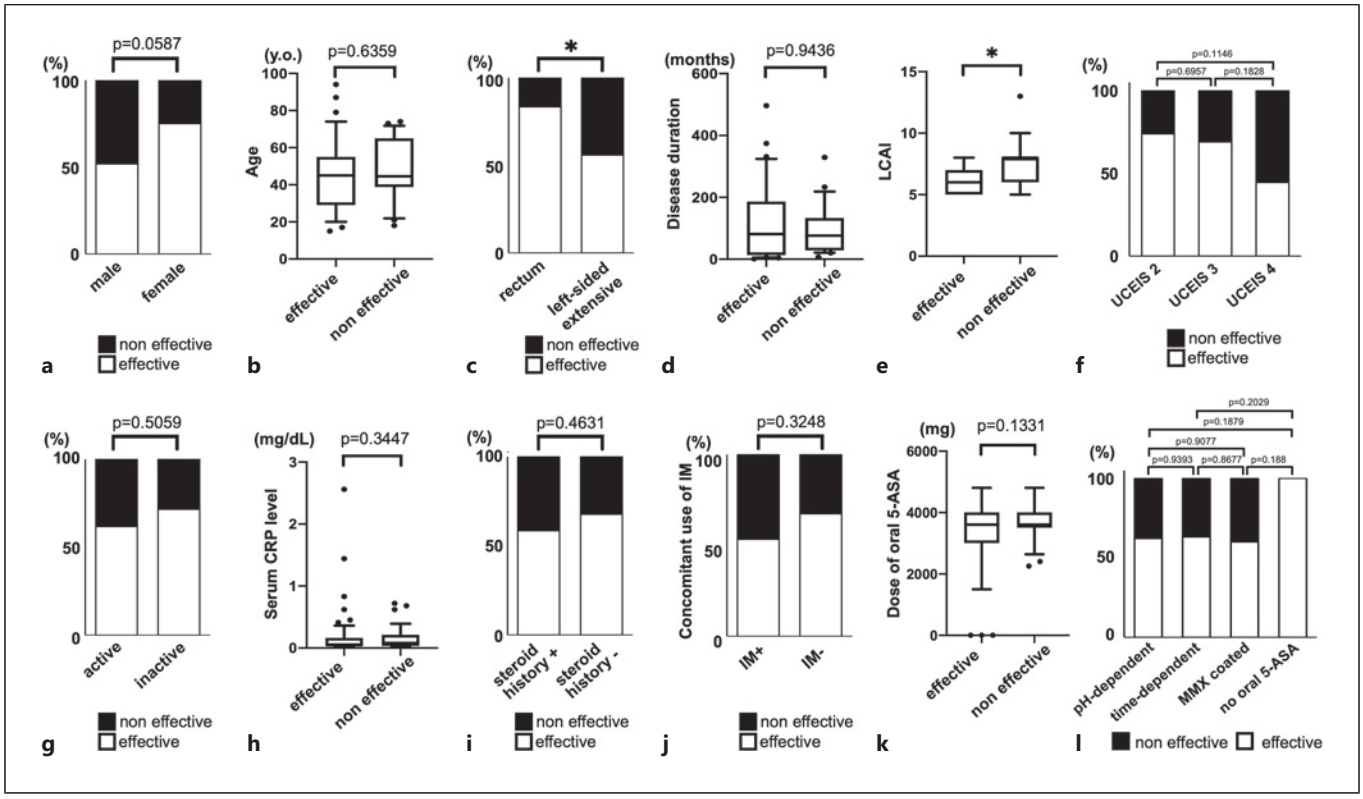

Fig. 1. Comparison of clinical background between the effective and non-effective groups. **a** Sex. **b** Age. **c** Disease type. **d** Disease duration. **e** LCAI. **f** Ulcerative Colitis Endoscopic Index of Severity (UCEIS). **g** Histological activity. **h** Serum CRP level. **i** History of steroid usage. **j** Concomitant use of immunomodulator. **k** Dosage of oral 5-ASA. **l** Type of oral 5-ASA at the time of the initiation of 5-ASA suppositories (*$p < 0.05$).

Table 2. Statistical analysis of clinical background factors affecting the effectiveness of 5-ASA suppositories

Clinical background	Single factor	*p* value	Multiple factors	*p* value
	OR (95% CI)		OR (95% CI)	
Sex	2.8 (0.949–8.262)	0.0587	2.68 (0.8381–8.5581)	0.0965
Age	1.65 (0.1724–15.862)	0.6539		
Disease duration	0.99 (0.9926–1.0027)	0.9436		
Disease type	3.55 (0.8902–14.13)	0.0412	3.09 (0.7092–13.4857)	0.1329
LCAI	3.94 (1.3065–11.8663)	0.0127	3.51 (1.1042–11.1512)	0.0333
Histological activity	1.55 (0.4228–5.6946)	0.5059		
Serum CRP	0.74 (0.1735–3.1860)	0.3447		
Usage of IM	0.55 (0.1687–1.8123)	0.3248		
History of oral steroid	1.48 (0.5134–4.3129)	0.4631		
Oral 5-ASA	1.00 (0.9999–1.0012)	0.1331		

treatment had the greatest influence on the efficacy of 5-ASA suppositories. Among the clinical factors investigated in this study, a low LCAI score at the time of treatment, disease type, and sex were considered in the multivariate model, which enabled a more accurate prediction of the treatment effect. In this study, we determined that an LCAI of less than 6, proctitis type, and female sex were clinical background factors that predicted high efficacy of 5-ASA suppositories. Our study is the first to examine the predictive ability of clinical background factors for the efficacy of 5-ASA suppositories, and the selection of patients who are

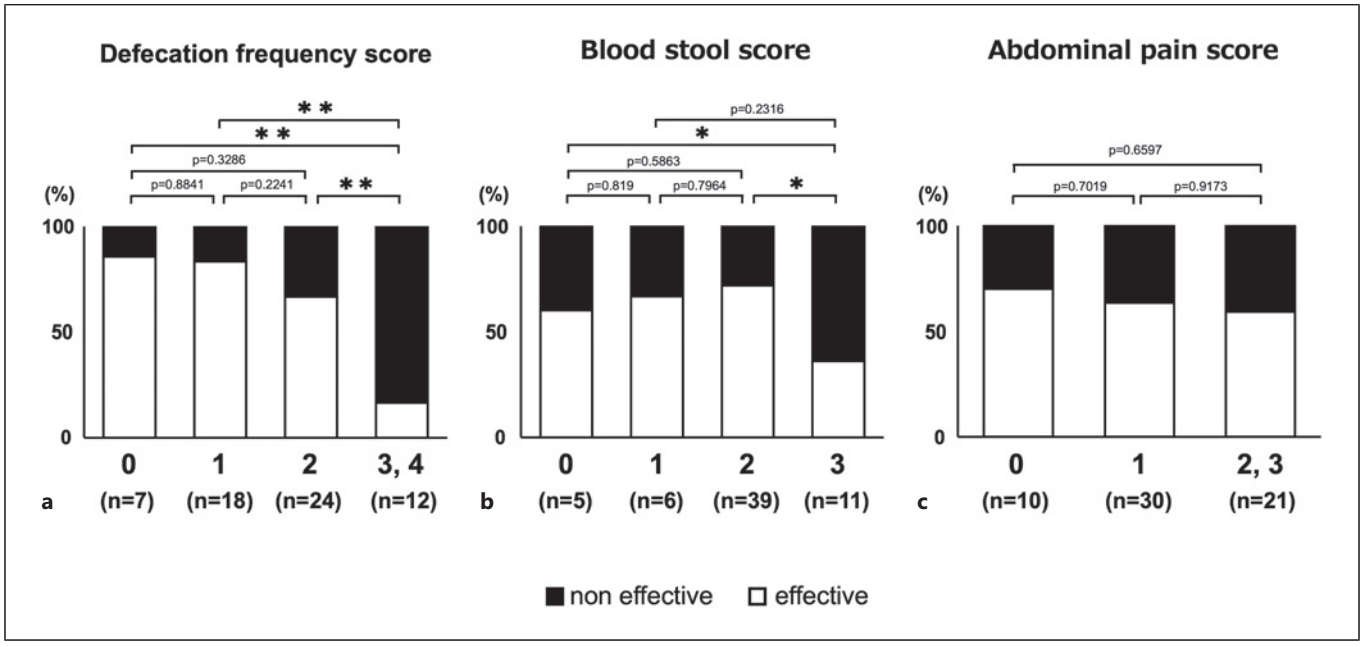

Fig. 2. Efficacy in each item of the LCAI. **a** Defecation frequency score. **b** Blood stool score. **c** Abdominal pain score (*$p < 0.05$, **$p < 0.005$).

predicted to show a high efficacy rate for 5-ASA suppositories may not only improve patient adherence but also provide a basis for physicians to prescribe 5-ASA suppositories with confidence.

The 5-ASA suppository is the first-line therapeutic agent for proctitis-type UC and has been reported to show better efficacy than foams and enema [21]. A direct comparison of the efficacy of oral mesalazine and mesalazine suppository for proctitis-type UC has been reported. A 4-week, randomized, single-blind study examined the efficacy of 800 mg oral mesalazine tablets three times a day versus 400 mg mesalazine suppository three times a day in 58 patients with proctitis-type UC. The results showed that improvement in disease activity scores and histological remission rates were significantly higher with the suppository than with the tablet at both 2 and 4 weeks [8]. Subsequent reports have shown that 5-ASA suppositories are more effective and have a faster effect than oral 5-ASA preparations on proctitis-type UC [4]. A comparison between the mesalazine suppository and topical steroid therapy has also been reported. Seventy-nine patients with distal UC were stratified according to the extent of the disease and randomized into one of the treatment groups. The effect of the mesalazine suppository group was statistically superior to that of the topical steroid group [22]. A meta-analysis also reported that 5-ASA suppositories were more effective than topical steroids [11].

In the present study, we investigated the clinical background of UC patients that were expected to influence the efficacy of 5-ASA suppositories. Our findings showed that female patients tended to have a higher effect of 5-ASA suppository treatment in comparison with males, although the difference was not statistically significant. A previous study also reported that non-adherent patients are more likely to be male [23]. In the present study, although we confirmed in the outpatient clinic that the 5-ASA suppositories were being used reliably, it is possible that the men did not have perfect adherence. Statistically significant differences in clinical background were also found in relation to the disease type, and the 5-ASA suppository was more effective in cases with the proctitis type than cases with the other disease types. A Japanese phase 3 multicenter, randomized, double-blind, placebo-controlled study on mesalazine suppository revealed a higher efficacy in proctitis ($p < 0.0001$) than pancolitis ($p = 0.0491$) and left-sided colitis ($p = 0.5455$) in comparison with a placebo [15]. In the present study, pre-treatment disease activity (LCAI) had the greatest influence on the effectiveness of the 5-ASA suppository. To date, the effectiveness of 5-ASA suppositories in relation to measures of disease activity, such as LCAI, has not been described. In this study, the use of a cutoff LCAI score of 7 showed significantly higher subsequent efficacy in patients with scores of 6 or less compared to those with scores of 7 or

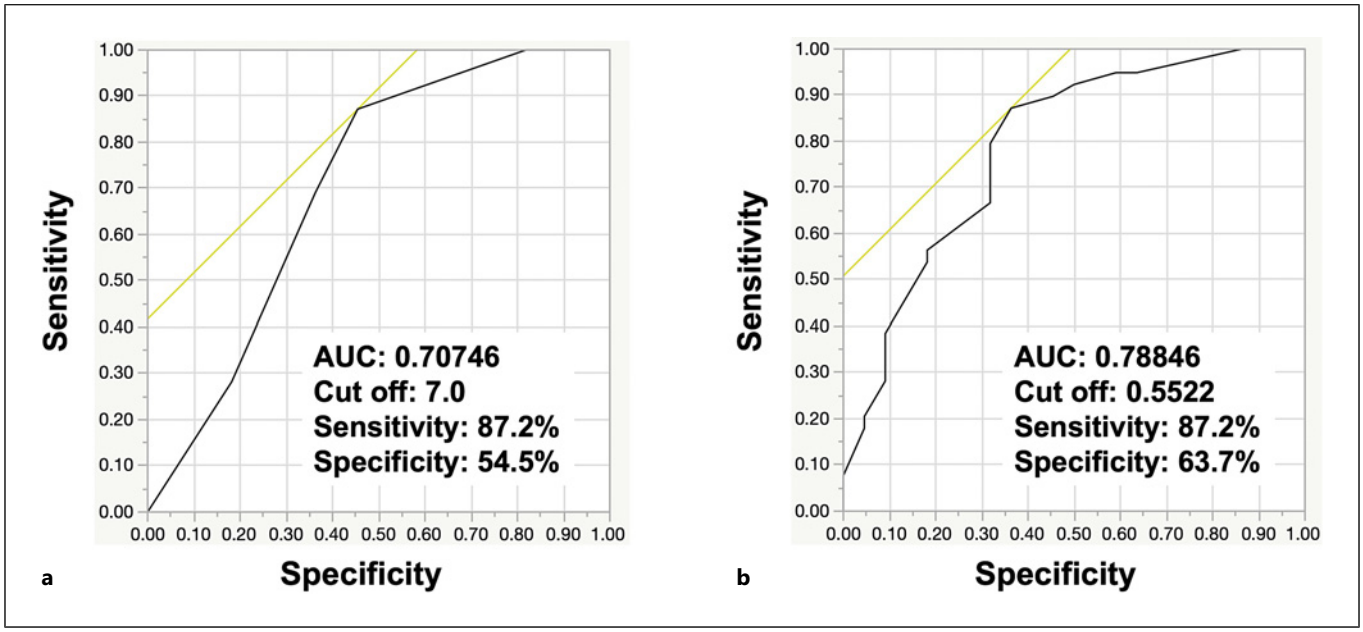

Fig. 3. Receiver operating characteristic curve analysis of the effective and non-effective groups. The area under the curve (AUC) was determined at a 95% confidence interval. **a** LCAI showed the most significant difference between the effective and non-effective groups in univariate analysis. **b** A multivariate model obtained by logistic regression analysis used LCAI, disease type, and sex to distinguish between the effective and non-effective groups (–5.2617 + 0.64911 × LCAI + (–0.5688 (female) or 0.5688 (male)) + (0.58855 (extensive or left-sided type) or –0.58855 (rectum))).

more. In addition, a multivariate model calculated by logistic regression analysis that included female sex, proctitis disease type, and an LCAI score of 6 or less showed a high predictive value for the effectiveness of 5-ASA suppository treatment. For each of the LACI items, the efficacy of 5-ASA suppositories decreased with increasing frequency of defecation and blood in the stool, and increased frequency of defecation was more significantly correlated with lower efficacy of 5-ASA suppositories. The limitation of this study includes the adherence of 5-ASA suppositories was only confirmed in an outpatient interview, the sample size is small, and the study was conducted in single center.

This study is the first attempt to extract the clinical background of patients with UC to predict the effect of the 5-ASA suppository. Although the efficacy of 5-ASA suppositories is not directly related to improved adherence, the results of this study suggest that explaining that 5-ASA suppositories are likely to be effective in indicated patients may improve patient's adherence.

Statement of Ethics

Opt-out informed consent protocol was used for use of participant data for research purposes. This consent procedure was reviewed and approved by Ethics Committee of the Kyoto Prefectural University of Medicine, approval number (ERB-C-610-4), date of decision (June 17, 2016). Those who rejected were excluded. This study was conducted following the ethical principles of the Declaration of Helsinki.

Conflict of Interest Statement

Y.N. received scholarship funds from EA Pharma. Co. Ltd., a collaboration research fund from Taiyo Kagaku Co., Ltd., and lecture fees from Mylan EPD Co., Takeda Pharma. Co., Ltd., Mochida Pharma. Co. Ltd., EA Pharma. Co. Ltd., Otsuka Pharma. Co. Ltd., and Miyarisan Pharma. Co. Ltd. This study was partly supported by these funds. Y.N. is an associate editor of "Digestion." Neither the funding agency nor any outside organization participated in the study design or had any competing interests. These companies approved the final version of the manuscript.

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Author Contributions

Designed the experiments and wrote the paper: Kazuhiko Uchiyama, Tomohisa Takagi, and Yuji Naito; analyzed the data: Tomohisa Takagi, Saori Kashiwagi, Yuki Minagawa, Makoto Tanaka, Yuma Hotta, Takeshi Sugaya, Ken Inoue, Kazuhiro Katada, Kazuhiro Kamada, Takeshi Ishikawa, Hiroaki Yasuda, Hideyuki Konishi, Mitsuo Kishimoto, Yuji Naito, Yoshito Itoh, and Kazuhiko Uchiyama; sample collection: Kohei Asaeda, Mariko Kubota-Kajiwara, Tomohisa Takagi, and Kazuhiko Uchiyama; manipulation of samples: Katsura Mizushima and Kazuhiko Uchiyama; overall supervision: Tomohisa Takagi, Yuji Naito, and Yoshito Itoh. All authors read and approved the final manuscript.

Data Availability Statement

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

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