


## ORIGINAL ARTICLE OPEN ACCESS

# History of Previous Medication Self-Discontinuation Predicts the Current Adherence to 5-Aminosalicylates in Patients With Ulcerative Colitis

Shogo Kitahata<sup>1</sup>  | Ayaka Nakamura<sup>1</sup> | Yuka Kimura<sup>1</sup> | Mai Fukumoto<sup>1</sup> | Kana Matsuoka<sup>1</sup> | Takuya Matsuda<sup>1</sup> | Kazuya Murakawa<sup>1</sup> | Taisei Murakami<sup>1</sup> | Kei Onishi<sup>1</sup> | Hirofumi Izumoto<sup>1</sup> | Kozue Kanemitsu-Okada<sup>1</sup> | Tomoe Kawamura<sup>1</sup> | Taira Kuroda<sup>1</sup> | Junko Matsuoka<sup>1</sup> | Fujimasa Tada<sup>1</sup> | Hideki Miyata<sup>1</sup> | Atsushi Hiraoka<sup>1</sup> | Kazuhiro Tange<sup>2</sup> | Yasunori Yamamoto<sup>3</sup> | Eiji Takeshita<sup>2</sup> | Yoshiou Ikeda<sup>3</sup> | Shinya Furukawa<sup>4</sup> | Eiji Tsubouchi<sup>1</sup> | Tomoyuki Ninomiya<sup>1</sup> | Yoichi Hiasa<sup>5</sup>

<sup>1</sup>Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Ehime, Japan | <sup>2</sup>Department of Inflammatory Bowel Diseases and Therapeutics, Ehime University Graduate School of Medicine, Matsuyama, Ehime, Japan | <sup>3</sup>Endoscopy Center, Ehime University Graduate School of Medicine, Matsuyama, Ehime, Japan | <sup>4</sup>Health Services Center, Ehime University, Matsuyama, Ehime, Japan | <sup>5</sup>Department of Gastroenterology and Metabolism, Ehime University Graduate School of Medicine, Matsuyama, Ehime, Japan

**Correspondence:** Shogo Kitahata ([shogo\\_kitahata@yahoo.co.jp](mailto:shogo_kitahata@yahoo.co.jp))

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## ABSTRACT

**Aim:** Medication adherence is critical in 5-aminosalicylate therapy for patients with ulcerative colitis. Patients with a history of previous medication self-discontinuation may continue to have low adherence due to the influence of inappropriate disease awareness. This study aimed to determine the association between the history of previous medication self-discontinuation and current adherence to 5-aminosalicylates in patients with ulcerative colitis.

**Methods and Results:** This cross-sectional study was conducted in Japan from 2021 to 2024. A self-administered questionnaire was used in 228 patients with ulcerative colitis who were taking 5-aminosalicylates. We defined adherence as consumption of  $\geq 80\%$  of the prescribed dose. Patients with a history of previous medication self-discontinuation were defined as having discontinued medication at least once in the past by their own judgment. The current adherence rate to 5-aminosalicylates in this study was 92.9% (212/228). The proportion of patients with a history of previous medication self-discontinuation was 7.8% (18/228). History of previous medication self-discontinuation ( $p < 0.001$ ), younger age ( $p < 0.001$ ), and once-daily 5-aminosalicylates regimen ( $p < 0.001$ ) were inversely associated with current adherence to 5-aminosalicylates.

**Conclusion:** History of previous medication self-discontinuation was inversely associated with current adherence to 5-aminosalicylates among patients with ulcerative colitis. The results of this study suggest that determining the history of previous medication self-discontinuation may be a valuable tool in assessing current adherence to 5-aminosalicylates, which can be cumbersome.

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## 1 | Introduction

5-Aminosalicylates (5-ASA) remain the standard of care for patients with mild and moderate ulcerative colitis (UC) [1, 2]. Patients with UC continue to take 5-ASA throughout their lives, even during periods of clinical remission [3, 4]. Non-adherence to 5-ASA is a risk factor for flares and colorectal cancer in patients with UC [5–7]. Therefore, adherence should be evaluated in 5-ASA therapy. However, assessing adherence to 5-ASA in daily practice is complicated [1]. Inappropriate patient awareness decreases medication adherence [8]. Moreover, adherence may not improve unless the inappropriate patient awareness is corrected. We hypothesized that a history of previous medication self-discontinuation would be inversely associated with current adherence to 5-ASA. Factors that have been shown to predict non-adherence to 5-ASA include age, sex, and environmental factors [9–16]. However, limited studies have assessed the impact of a history of previous medication self-discontinuation on the risk of current adherence to 5-ASA. This study aimed to determine the association between a history of previous medication self-discontinuation and current adherence to 5-ASA in patients with UC.

## 2 | Methods

### 2.1 | Participants

Between 2021 and 2024, 239 patients with UC who attended Ehime Prefectural Central Hospital (Ehime, Japan) excluding those patients who were not taking 5-ASA preparations were enrolled. All the patients who were able to consent to this study and respond to the self-administered questionnaire about the history of previous medication self-discontinuation and adherence were considered candidates. The diagnosis of UC was based on established clinical, radiographic, endoscopic, and histopathologic criteria [17]. All the patients had been taking 5-ASA for at least 2 months. Those with previous colostomy and ileostomy, total or subtotal colorectal resection, or those with incomplete data were excluded. Ultimately, 228 patients were enrolled in this cross-sectional study (Figure S1).

### 2.2 | Evaluation of UC Disease Activity

Clinical remission (CR) was indicated by a partial Mayo score  $\leq 1$  [18]. The partial Mayo score was obtained from medical records on the day medication adherence was assessed. In our hospital, patients fill out certain partial Mayo score items (bloody stool and diarrhea) at each outpatient visit. The physician will then fill out the physician's global assessment. Based on endoscopic investigations performed before entry into the study and medical history, patients with UC were classified as E1 (proctitis), E2 (left-sided colitis), or E3 (pancolitis), according to the Montreal Classification, and depending on the extent of the lesions [19].

### 2.3 | Definition of Adherence

Patients were asked to complete a self-administered questionnaire regarding the type of 5-ASA tablet and regimen,

number of missed doses, and history of previous medication self-discontinuation to determine their adherence to 5-ASA (Table). Based on previous studies, we investigated the rate of adherence to 5-ASA during the 7 days prior to enrollment to reduce the possibility of recall bias in the self-reports [2]. We defined adherence as consumption of  $\geq 80\%$  of the prescribed dose [1]. Patients with a history of previous medication self-discontinuation were defined as having discontinued oral medicine containing a 5-ASA by their own judgment without medical justification at least once in the past.

### 2.4 | Statistical Analyses

All statistical analyses were performed using Easy-R (EZR) version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact and Wilcoxon rank-sum tests were used to compare nominal and continuous variables, respectively. To evaluate the discriminative ability of age to detect adherence to 5-ASA, a receiver operating characteristic (ROC) curve was generated, and the area under the ROC curve (AUC) was calculated. The participants were divided into younger and older age groups based on cutoff values. Statistical significance was set at  $p < 0.05$ .

### 2.5 | Ethical Considerations

The study protocol was developed in accordance with the 1964 Declaration of Helsinki and subsequent ethical guidelines. All the participants provided written informed consent. This study was approved by the Institutional Ethics Committee of Ehime Central Hospital (approval no. 03-57).

## 3 | Results

The clinical characteristics of patients with UC and the answers to the questionnaire are summarized in Table 1. The current adherence to 5-ASA rate in this study was 92.9% (212/228). The proportion of patients with a history of previous medication self-discontinuation was 7.8% (18/228). To identify factors associated with current adherence, patients were classified into two groups: those demonstrating current adherence ( $n = 212$ ) and those demonstrating current non-adherence ( $n = 16$ ) (Table 2). No significant between-group differences were found with regard to sex, clinical remission, or C-reactive protein levels. Patients with current non-adherence to 5-ASA were significantly younger than those with current adherence ( $p = 0.001$ ). ROC analysis was performed to assess the discriminative ability of age to detect adherence to 5-ASA. The cutoff value for age was 45 years, with a sensitivity and specificity of 0.67 and 0.81 (AUC: 0.73, 95% CI: 0.60–0.86) (Figure S2). Younger age ( $< 45$  years) was inversely associated with current adherence ( $p < 0.001$ ). The prevalence of current adherence in the once-daily 5-ASA regimen group was significantly lower than in the twice-daily or more-daily 5-ASA regimen group ( $p < 0.001$ ). A significantly lower prevalence of current adherence was observed in patients with a history of previous medication self-discontinuation than in those without a history of previous medication self-discontinuation ( $p < 0.001$ ).

#### 4 | Discussion

This study revealed that a history of previous medication self-discontinuation, younger age, and a once-daily 5-ASA regimen were inversely associated with current adherence to 5-ASA. This is the first study to demonstrate the negative association

between a history of previous medication self-discontinuation and current adherence to 5-ASA in patients with UC.

In our study, the percentage of patients with adherence to 5-ASA was 92.9%. Previous studies have reported percentages of adherence to 5-ASA ranging from 40% to 93% [9–16]. The discrepancy in the reported percentage of adherence to 5-ASA was at least partly attributed to the sample size, age, sex, definition of medication adherence, and differences in socioeconomic background [2, 20].

Three studies have reported an association between age and adherence to 5-ASA among patients with UC. An observational study of 274 patients with UC in Spain reported that younger age was inversely associated with adherence to 5-ASA [12]. A Canadian study on 1681 patients with UC reported that in addition to younger age, female sex and current non-use of corticosteroids were inversely associated with adherence to 5-ASA [13]. Moreover, a Korean multicenter, cross-sectional study, younger age, alcohol consumption, and current smoking were inversely associated with adherence to 5-ASA [14]. Individuals of a younger age are more involved in academics and work, which may affect adherence to 5-ASA [14].

Some studies have reported an association between 5-ASA regimens and adherence to 5-ASA among patients with inflammatory bowel disease (IBD). A study in Germany involving 362 patients with UC reported that once-daily 5-ASA regimens had better remission rates, acceptability, and adherence compared with twice-daily 5-ASA regimens [21]. Two studies have been

**TABLE 1** | Baseline patient characteristics and the answers to the questionnaire.

Variable	UC (N=228)
Age, years <sup>a</sup>	50 (36–60)
Male (%)	120 (52.6)
Types of 5-ASA (Pentasa granules/ Pentasa tablets/Asacol/Lialda/ Salazopyrin)	58/18/55/63/34
Prescribed 5-ASA regimen (once-daily/ twice-daily/more)	106/70/52
Number of missed doses (0/1/2/3/4/≥ 5)	130/61/26/7/1/3
Current adherence	212 (92.9)
History of previous medication self-discontinuation (%)	18 (7.8)

Abbreviations: 5-ASA, 5-aminosalicylate; UC, ulcerative colitis.

<sup>a</sup>Median (interquartile range).

**TABLE 2** | Analysis of association factors contributing to current adherence.

Variable	UC		p-value
	Current adherence (N=212)	Current non-adherence (N=16)	
Age, years <sup>a</sup>	51 (38–60)	32 (27–43)	0.001
Younger age (< 45 years) (%)	70 (33.0)	13 (81.2)	< 0.001
Male (%)	113 (53.3)	7 (43.7)	0.605
Disease extent (pancolitis/left-sided/ proctitis)	102/55/55	7/3/6	
Medication			
Prescribed 5-ASA regimen (once-daily/twice-daily or more)	91/121	15/1	< 0.001
Prednisolone (%)	21 (9.9)	0 (0.0)	0.373
Immunomodulators (%)	27 (12.7)	0 (0.0)	0.228
Biologic agents (%)	28 (13.2)	2 (12.5)	1
Clinical remission (%)	129 (60.8)	13 (81.2)	0.118
CRP, mg/dL <sup>a</sup>	0.06 (0.02–0.17)	0.06 (0.04–0.11)	0.902
History of previous medication self-discontinuation (%)	11 (5.1)	7 (43.7)	< 0.001

Note: The Wilcoxon rank-sum test was used to compare age and CRP levels between patients with UC with current adherence and those with current non-adherence. Fisher's exact test was used to compare sex, treatment, clinical remission, history of previous medication self-discontinuation between patients with UC with current adherence and those with current non-adherence.

Abbreviations: 5-ASA, 5-aminosalicylate; CRP, C-reactive protein; UC, ulcerative colitis.

<sup>a</sup>Median (interquartile range).

reported in the United Kingdom involving 98 patients with IBD and 58 patients with UC [15, 22]. Both studies reported that three-time daily 5-ASA regimens were a predictor of non-adherence [15, 22]. In contrast to previous reports, this study showed that once-daily 5-ASA regimens were associated with current non-adherence compared with twice-daily or more-daily 5-ASA regimens. Based on previous reports, our hospital actively recommends a once-daily 5-ASA regimen for patients suspected of non-adherence. Therefore, selection bias could have affected the results of the 5-ASA regimen.

Besides age and prescribed 5-ASA regimen, other factors have also been reported to be associated with adherence to 5-ASA in patients with UC [15, 16]. However, previous studies have not reported an association between history of previous medication self-discontinuation and adherence to 5-ASA in patients with UC. In patients with UC during pregnancy, 46.5% of patients self-discontinued medication because of inappropriate disease awareness about the safety and teratogenic effects of medications [23]. History of previous medication self-discontinuation may have been the result of a significant decline in adherence and may reflect inappropriate disease awareness [3]. Unless corrected, inappropriate disease awareness may also affect current adherence to 5-ASA [3]. The results of our study suggest that there should be greater attention toward adherence to 5-ASA in patients with UC with a history of previous medication self-discontinuation.

Nonetheless, this study has certain limitations. First, we could not establish a causal relationship between the history of previous medication self-discontinuation and current adherence to 5-ASA in patients with UC. Prospective studies are warranted to investigate these causal relationships. Second, this study did not include a control group. Third, validated scales such as the Medication Adherence Report Scale and the Morisky Medication Adherence Scale were not used to assess adherence [24, 25]. Our self-administered questionnaire may have been affected by recall bias because it relied solely on patient memory. However, this effect was minimized in the present study because we investigated the rate of adherence to 5-ASA during the 7 days prior to enrollment [2]. Fourth, we did not consider the use of other drugs or environmental factors such as financial burden, employment status, and family structure. Fifth, reasons for the history of previous medication self-discontinuation were not evaluated. Sixth, we were unable to conduct multivariate analyses because of the small number of paired events (current non-adherence). Seventh, we did not consider previous infection with coronavirus disease 2019 (COVID-19), a potential factor for poor therapeutic adherence, even though our study spans the period of the COVID-19 pandemic [26]. Finally, this was a single-center study and was not representative of Japanese patients with UC. In this study, more than half of the patients (142/228) were in clinical remission, which may not adequately reflect the adherence of patients with UC in the active phase. However, no significant difference was observed between patients' remission status and adherence. In addition, the median age, sex ratio, and frequency of drug use were similar to those in previous national surveys of UC in Japan [27].

In conclusion, the history of previous medication self-discontinuation was inversely associated with current adherence

to 5-ASA among patients with UC. The results of this study suggest that determining the history of previous medication self-discontinuation may be a valuable tool in assessing current adherence to 5-ASA, which can be cumbersome.

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## Ethics Statement

The study protocol was developed in accordance with the 1964 Declaration of Helsinki and subsequent versions of the ethical guidelines. This study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (approval no. 03-57).

## Consent

All participants provided written informed consent.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

The data supporting the findings of this study are available from the corresponding author, SK, upon reasonable request.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.