Original Article

Retrospective investigation of mesalamine intolerance in patients with ulcerative colitis

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Mesalamine is a key drug in the treatment of ulcerative colitis (UC) for both induction and maintenance therapy. On the other hand, it is known that there are some cases of mesalamine intolerance that are difficult to distinguish from symptoms due to aggravation of UC. The aim of this study is to investigate the clinical characteristic of mesalamine intolerance in UC. A retrospective, observational study was conducted. We enrolled 31 patients who were diagnosed as mesalamine intolerance between April 2015 to March 2020. We examined clinical features, time to onset, drug types of mesalamine, DLST positive rate, colonoscopy findings, disease activity, and clinical course after diagnosis. The average dose of mesalamine was 3.69 g and DLST-positive was 57.1%. Within the first 2 weeks from the start of mesalamine, 51.6% showed symptoms of intolerance. The serum CRP level was relatively high at ≥10.0 mg/dl in 53.6% of the cases. There was no difference in clinical background, symptoms, or laboratory findings between patients with DLST-positive and negative. In this study, we clarified the clinical characteristics of mesalamine intolerant patients, and found no difference in the clinical background or success rate of desensitization therapy between positive and negative DLST cases.

***Key Words*: mesalamine, intolerance, ulcerative colitis, CRP**

Mesalamine has been developed as a salazosulfapyridine (SASP) free of sulfapyridine and has various side effects. As a first-line medication to induce and maintain remission in patients with ulcerative colitis (UC), mesalamine is a key drug due to its efficacy and safety in several clinical trials.[1–5] Most patients with UC with mild to moderate activity can induce disease remission only with mesalamine treatment[5] and continuous use of mesalamine can contribute to the maintenance of disease remission.[6] However, it is well known that mesalamine intolerance occurs in certain patients whose symptoms are difficult to distinguish from symptoms due to UC aggravation, such as fever, diarrhea, and bloody stool.[7–11] It has been reported that 4.6% and 1.4% of patients presented with diarrhea and bloody stool, respectively, as a symptom of mesalamine intolerance.[2] In addition, extraintestinal lesions, such as arthritis,[12,13] vasculitis rash,[12] pancreatitis,[13] pericarditis,[14] pericardial effusion,[15] Kawasaki-like syndrome,[16] and lupus-like syndrome,[17] have been reported as symptoms of mesalamine intolerance. As mesalamine treatment is essential for UC induction and maintenance therapy, the decision to withdraw mesalamine due to intolerance should be made carefully and accurately. However, only a few studies on mesalamine intolerance have been reported, and the clinical characteristics of mesalamine intolerance have not been well elucidated.

Drug-induced lymphocyte stimulation test (DLST) is widely used to diagnose drug allergies[18] to measure ^{3}H-thymidine uptake by proliferating lymphocytes following stimulation with the drug of interest. However, the problem of DLST has been reported as false-positive and false-negative, and the variation in its diagnosis depends on the drug.[19–21] Regarding the investigation of mesalamine intolerance, DLST has been reported to show low sensitivity and high specificity, suggesting its usefulness for a definitive diagnosis.[22] However, in clinical situations, it is often the case that there is not enough time to obtain the results of DLST to diagnose mesalamine intolerance. To date, there have been no reports demonstrating the difference in clinical symptoms of mesalamine intolerance due to the results of DLST.

This study aimed to demonstrate the clinical characteristics of mesalamine intolerance and investigate the difference between patients with DLST-positive and DLST-negative to elicit caution regarding the treatment of UC with mesalamine.

Materials and Methods

Patients. A total of 373 UC patients attended the gastroenterology outpatient clinic at the Kyoto Prefectural University of Medicine Hospital from April 2015 to March 2020. Among them, 31 patients (8.3%) were diagnosed with mesalazine intolerance. Clinical characteristics, such as the duration of the onset of intolerance symptoms, clinical symptoms of intolerance, and blood test findings, were investigated. The study protocol was approved by the Ethics Committee of the Kyoto Prefectural University of Medicine (ERB-C-610-1). This study was conducted following the ethical principles of the Declaration of Helsinki.

Definition of mesalamine intolerance. Patients with symptoms of UC exacerbation-like symptoms, such as abdominal pain, diarrhea, bloody stool, and fever, and extraintestinal symptoms, such as skin rash and joint pain, after the administration of mesalamine and whose symptoms have improved within 5 days by stopping the administration of mesalamine. Fever was defined as a condition in which a fever of ≥38.0°C lasted for at least 3 days, and other causes, such as infection, could be ruled out. Diarrhea and bloody stool were defined as the number of times per day that increased compared to before the administration of mesalamine, and at least five times a day was observed.

DLST. DLST was performed in 21 of 31 patients with mesalamine intolerance, and the clinical background was compared between patients with DLST-positive and DLST-negative.

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Endoscopic evaluation. Among the 31 cases, 28 underwent colonoscopy within a week of symptom onset. The Mayo endoscopic subscore (MES) was used to evaluate the endoscopic severity of UC.

Assessment of clinical activity. Clinical disease activities were determined using the Lichtiger Colitis Activity Index (LCAI)[23] for clinical activity at the onset of intolerance symptoms.

Statistical analysis. The analysis of variance (ANOVA) was performed to assess the trend of the mean, stratified according to the normally distributed continuous variables; the trend test was based on liner contrast. All analyses were performed with JMP PRO ver. 14.0.0 (SAS Institute Japan Ltd., Tokyo, Japan). Continuous data were described as mean ± SD, if normally distributed, or median and interquartile range IQR (25%, 75%), if not normally distributed.

Results

Background of patients. A summary of the clinical background of the patients is shown in Table 1. The details of each case regarding the type of disease, type and dose of mesalamine, and the results of DLST are shown in Table 2. The average dose of mesalamine was 3.69 g (time-dependent: 3.64 g, pH-dependent: 3.54 g, multi-matrix: 4.8 g) and DLST-positive was 57.1% (12/21 cases) and DLST-negative was 42.9% (9/21).

Time of onset. Within the first 2 weeks from the start of mesalamine, approximately half of the patients (51.6%) showed symptoms of intolerance, and approximately three-fourths (77.4%) of the patients showed symptoms within 28 days (Fig. 1).

Table 1. Patient characteristics and background

Total number		31
Sex (female/male)		14/17
Age (years)		46.0 (19–72)
Disease duration (month)		77.0 (2–347)
Smoking history (%)		8 (17.0)
Disease location (%)	Extensive	24 (77.4)
	Left-sided	6 (19.4)
	Rectum	1 (3.2)
Current medication (%)		
Mesalamine (%)	Time-dependent release	19 (61.3)
	pH-dependent release	10 (32.3)
	Multi-matrix	2 (6.4)
	Steroid	4 (12.9)
	Thioprine	0 (0.0)
	Biologics	1 (3.2)
	GMA	2 (6.4)

Table 2. The detail of enrolled patients

Case	Sex	Age	Disease type	Type of mesalaizne	Dose of mesalazine (g)	DLST	Duration to DLST (days)	S.I.
1	F	65	Rectum	Time-dependent	4	—		
2	F	50	Pan	Time-dependent	4	—		
3	F	56	Pan	Time-dependent	4	Positive	25	17.8
4	M	52	Left-sided	Time-dependent	4	—		
5	M	28	Pan	pH-dependent	3.6	—		
6	F	63	Left-sided	Time-dependent	4	Negative	12	1.4
7	M	79	Pan	pH-dependent	3	Negative	7	1.7
8	M	50	Pan	Time-dependent	1.25	Positive	12	2.5
9	F	55	Pan	Time-dependent	4	Negative	22	1.2
10	M	64	Pan	pH-dependent	3.6	—		
11	F	30	Pan	pH-dependent	3.6	Negative	14	1.1
12	M	52	Pan	Time-dependent	4	—		
13	F	54	Pan	Time-dependent	4	—		
14	M	25	Pan	Time-dependent	2	Negative	20	1.3
15	F	33	Pan	pH-dependent	3.6	Positive	18	2.7
16	M	50	Left-sided	Time-dependent	2	Negative	30	1.4
17	F	62	Left-sided	pH-dependent	3.6	Positive	20	1.9
18	F	52	Pan	pH-dependent	3.6	Negative	28	1.6
19	M	33	Left-sided	pH-dependent	3.6	Positive	10	3.4
20	M	26	Pan	Time-dependent	4	Positive	13	8.2
21	M	26	Pan	Time-dependent	4	Negative	7	1.2
22	F	22	Pan	Time-dependent	4	Positive	21	4.2
23	F	35	Pan	Time-dependent	4	Positive	7	2.4
24	M	22	Pan	Multi-matrix	4.8	Negative	7	1.5
25	M	20	Pan	pH-dependent	3.6	Positive	14	20.1
26	M	20	Pan	pH-dependent	3.6	Positive	14	5.3
27	M	42	Pan	Time-dependent	4	—		
28	M	46	Pan	Time-dependent	4	Positive	28	1.9
29	F	22	Pan	Time-dependent	4	—		
30	F	47	Left-sided	Time-dependent	4	—		
31	M	73	Pan	Multi-matrix	4.8	Positive	13	2

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Symptoms of intolerance. Among the symptoms of mesalamine intolerance, fever, abdominal pain, diarrhea, and bloody stool were common, and the incidences of these symptoms were 83.9%, 74.2%, and 71.0%, respectively. There were only a few cases of skin rash, joint pain, headache, pancreatitis, and liver dysfunction, and the incidences of these symptoms were 12.9%, 3.2%, 3.2%, 3.2%, and 3.2%, respectively (Fig. 2).

Serum CRP level. The serum CRP level at the time of symptom appearance was relatively high at ≥10.0 mg/dl in 53.6% of the cases (Fig. 3).

Endoscopic evaluation. Colonoscopy was performed in 28 patients, and among them, of which 1 (3.6%), 20 (71.4%), and 7 (25.0%) were diagnosed with MES 1, 2, and 3, respectively (Fig. 4).

Comparison of DLST-positive and DLST-negative. A summary of the comparison of clinical background between patients with negative and positive DLST is shown in Table 3. DLST was performed in 21 patients, 9 (42.9%) were negative and 12 (57.1%) were positive. The period from the start of the administration to the onset of symptoms was compared between the DLST-negative group (14.0 days) and the DLST-positive group (15.0 days), and no statistical differences were observed at each time point. There were also no statistically significant differences between the DLST-negative and DLST-positive groups in terms of the period from discontinuation of treatment to improvement in symptoms. Regarding the ratio of symptoms of mesalamine intolerance, such as fever, abdominal pain, diarrhea, bloody stool, skin rash, joint pain, headache, pancreatitis, and liver dysfunction, no significant differences were observed between the two

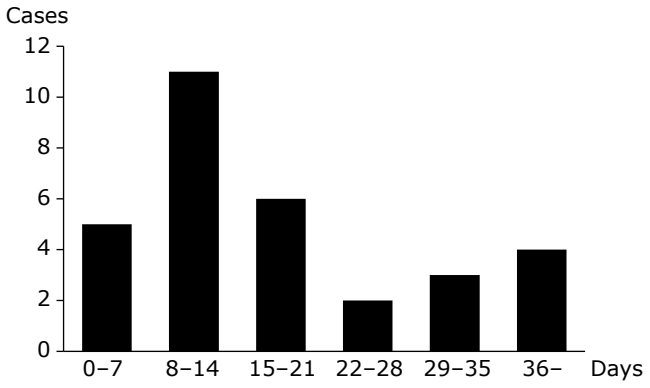

Fig. 1. Distribution of time to onset of symptoms.

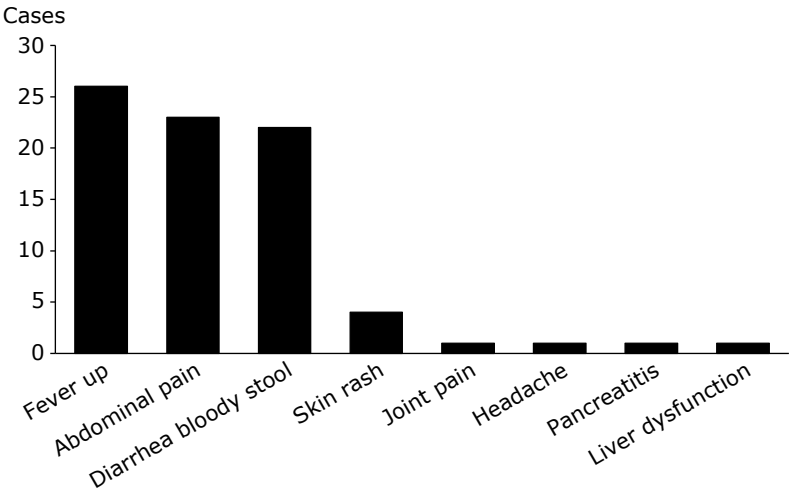

Fig. 2. Types of symptoms and their frequency of occurrence.

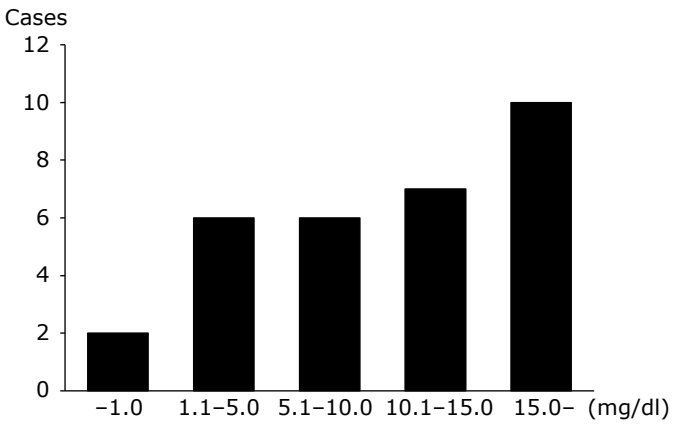

Fig. 3. Distribution of serum CRP levels in the presence of symptoms.

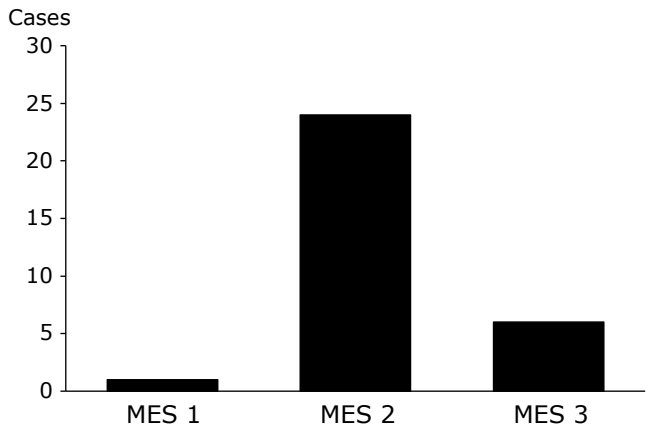

Fig. 4. Endoscopic severity in the presence of symptoms.

Table 3. Clinical background of DLST negative and positive patients

		DLST negative (n = 9)	DLST positive (n = 12)	p value
Sex (female/male)		4/5	7/5	0.52
Age (years)		45.5 (22–72)	40.6 (19–70)	0.57
Disease duration (months)		97.1 (68–132)	89.7 (5–219)	0.38
Disease location (Extensive/Left-sided/Rectum)		8/1/0	9/3/0	0.42
Period from start of administration to onset of symptoms (day)		14.0 (7–95)	15.0 (1–120)	0.41
Period from discontinuation of treatment to improvement of symptoms (day)		5.0 (1–13)	2.0 (1–18)	0.81
Symptoms (%)				
	Fever up	88.9 (8/9)	83.3 (10/12)	0.72
	Abdominal pain	66.7 (6/9)	75.0 (9/12)	0.68
	Diarrhea, bloody stool	66.7 (6/9)	75.0 (9/12)	0.68
	Skin rash	0.0 (0/9)	16.7 (2/12)	0.2
	Joint pain	11.1 (1/9)	0.0 (0/12)	0.24
	Headache	0.0 (0/9)	0.0 (0/12)	—
	Pancreatitis	0.0 (0/9)	8.3 (1/12)	0.37
	Liver dysfunction	0.0 (0/9)	0.0 (0/12)	—
MES (%)				
	0	0.0 (0/9)	0.0 (0/12)	—
	1	0.0 (0/9)	8.3 (1/12)	0.35
	2	88.9 (8/9)	75.0 (9/12)	0.09
	3	11.1 (1/9)	16.7 (2/12)	0.18
Lichtiger CAI index		10 (7–14)	10 (6–15)	0.87
CRP (mg/dl)		11.6 (0.01–19.8)	9.6 (0.2–19.7)	0.46

Table 4. The clinical course of the patients treated with mesalamine desensitization therapy

Case	Sex	Age	Disease type	DLST	Type of mesalamine at desensitization	Efficacy of desensitization	Observation period to final doses (day)	Final dose of mesalamine
11	F	30	Extensive	Negative	SASP	Success	60	3,000 mg
15	F	33	Extensive	Positive	SASP	Success	40	4,000 mg
16	M	50	Left-sided	Negative	pH-dependent	Failure	NA	NA
17	F	62	Left-sided	Positive	pH-dependent	Success	60	3,600 mg
21	M	26	Extensive	Negative	SASP	Success	70	4,000 mg
23	F	35	Extensive	Positive	Time-dependent	Success	60	4,000 mg
25	M	20	Extensive	Positive	Time-dependent	Success	90	4,000 mg

groups. The constitution of the endoscopic evaluation by MES did not show differences between the two groups. There were no differences between the two groups in clinical severity evaluated by LCAI (DLST-negative, 10; DLST-positive, 10) and the serum CRP level was 11.6 and 9.6 mg/dl in the DLST-negative and DLST-positive groups, respectively. As shown in Table 3, there was no difference in clinical background, symptoms, or laboratory findings between patients with DLST-positive and DLST-negative. The period between the appearance of intolerance symptoms and the evaluation of DLST was shown in Table 2 as duration to DLST. The mean time to DLST evaluation for DLST-positive patients was 16.2 days and that for negative patients was 16.3 days, showing no difference. We also investigated the correlation between Stimulation Index (S.I.) in DLST and clinical background factors. There was no correlation between S.I. and CRP level as blood test data, and between S.I. and CAI as 5-ASA intolerance symptoms. The results are presented in Supplemental Fig. 1*.

Desensitization therapy. Seven of the patients examined by DLST underwent subsequent desensitization therapy. Of these, three patients were DLST-negative and two successfully responded to desensitization therapy, and four were DLST-positive and all successfully responded to desensitization therapy (Table 4).

Discussion

This study showed 8.3% (31/373) of mesalamine intolerance in patients with UC, and the ratio is almost the same as the recent real-world data from a multicenter survey[11] demonstrating 11% (67/633) of mesalamine intolerance. Mesalamine allergy is strictly defined as DLST-positive, but many patients are clinically intolerant even with DLST negativity. The positive rate of DLST for drug allergy has been reported to be approximately 40%.[24] However, the clinical characteristics of DLST-positive and DLST-negative patients with UC who show symptoms of mesalamine intolerance are unclear. To our knowledge, this is the first study to compare the differences in clinical symptoms between DLST-positive and DLST-negative patients with UC.

Previous reports[25] have shown that mesalamine allergy is characterized by elevated levels of CRP at the onset of the disease and the absence of eosinophilia in the peripheral blood.

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In this study, the mean serum CRP level was 12.58 mg/dl, and 15 cases (48.4%) with a high level of ≥10 mg/dl and no peripheral eosinophilia were also observed. Fever, headache, pruritic rash, nausea, vomiting, and indigestion are some of the common side effects of mesalamine intolerance. Hepatotoxicity,[26,27] pancreatitis,[28,29] interstitial nephritis,[30,31] pneumonia,[32] and pericarditis[12,33] have been reported as rare but serious symptoms of mesalamine intolerance. The frequency of these side effects does not increase with increasing mesalamine dose,[34] but these symptoms are always dose-dependent and have been reported to resolve with decreasing dose.[35] The frequency of fever (85.7%), a typical symptom of 5-ASA intolerance, observed in this study was comparable to that reported in recent years (93.0%).[36] In addition, the clinical course of the cases in this study was similar to previous reports in that symptoms appeared within 2 weeks and serum CRP levels were high.[25,36]

DLST, also referred to as the lymphocyte transformation test (LTT), is used to identify adverse drug reactions. Since DLST has low sensitivity and high specificity for diagnosing mesalamine allergy, it is considered appropriate to use DLST rather than an exclusionary diagnosis for its definitive diagnosis. It has been reported that 6 of 24 cases (25%),[22] and 6 of 23 cases (26.1%)[11] of the patients with the symptoms of mesalamine intolerance showed positive of DLST. In the present study, 21 cases were performed DLST and 12 cases showed positive (57.1%). The reason about the high ratio of DLST-positive cases in this study is not clear, but we think that the DLST positivity rate in cases with the symptoms of mesalamine intolerance is difficult to compare simply with previous reports, since conditions such as timing of sample collection and other medications may be different. As there are also a certain number of false-negative cases that also exist in clinical practice,[22] the diagnosis of allergy should be based on the evaluation of the clinical course. The timing of DLST is also important, and it has also been reported that the time from the onset of allergic symptoms to blood collection is significantly longer in patients with mesalamine DLST-positive than in patients with DLST-negative.[36] When an allergic hypersensitivity reaction occurs, memory T cells proliferate unevenly, and regulatory T cells are strongly activated. As DLST is based on the response of memory T cells, the test can be falsely negative in this situation. Therefore, DLST should be performed after the allergic reaction is in remission or after 4 weeks.[37,38] The combination of steroids[39] or adalimumab[40] has been reported to prevent accurate results from DLST for mesalamine allergy. DLST detects type IV allergies associated with T lymphocytes, but adalimumab also suppresses T lymphocytes. Therefore, adalimumab may have masked mesalamine allergy and alleviated symptoms.[40] In this study, since there were only four cases of concomitant use of steroids and all had positive DLST results, concomitant use of steroids is thought to have no effect on the DLST results. In the present study, seven patients were treated with desensitization therapy. Although the number of cases was limited, the success rate was not affected by the results of DLST or desensitization therapy. A recent report also showed that the success rate of the desensitization treatment was not related to the results of DLST, which was similar to the course of this study.[36]

In this study, there was no difference in the type of symptoms, frequency of occurrence, or subsequent clinical course between DLST-positive and DLST-negative patients. This result indicate that clinical course and subsequent desensitization therapy could not be influenced by the results of DLST in patients with mesalamine intolerant. There have been no reports discussing differences in clinical symptoms according to DLST results in patients with UC with clinically diagnosed mesalamine intolerance; this is the first report to demonstrate this.

Author Contributions

Designed the experiments and wrote the paper: YM, KU, TT, and YN; analyzed the data: TT, SK, YH, MT, YH, NY, KI, KKatada, KKamada, TI, HY, HK, YN, YI, and KU; sample collection: YM, KA, MKK, TT, and KU; manipulation of samples: KM and KU. Overall supervision: KU, TT, YN, and YI. All authors read and approved the final manuscript.

Acknowledgments

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Abbreviations

DLST	drug-induced lymphocyte stimulation test
LCAI	Lichtiger Colitis Activity Index
MES	Mayo endoscopic subscore
SASP	salazosulfapyridine

Conflict of Interest

Kazuhiko Uchiyama received lecture fee from Mitsubishi Tanabe Pharma Corporation. Tomohisa Takagi received collaboration research funds from Sumitomo Seika Chemicals Co. Ltd. and received lecture fees from Mochida Pharma. Co. Ltd. and Janssen Pharma. K.K. Yuji Naito 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. Yoshito Itoh received lecture fee from AbbVie GK, research fund from AbbVie GK, Takeda Pharma. Co., Ltd., and EA Pharma. Co. Ltd. Yuji Naito 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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