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Randomised clinical trial: evaluation of the efficacy of mesalazine (mesalamine) suppositories in patients with ulcerative colitis and active rectal inflammation – a placebo-controlled study

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SUMMARY

Background
Mesalazine suppositories are recommended and widely used as the standard therapy in induction and maintenance of remission for proctitis.

Aim
To evaluate the efficacy of mesalazine suppositories in patients with ulcerative colitis (UC) and rectal inflammation; and in patient groups categorised by the extent of lesions.

Methods
This study was a phase III multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Mild-to-moderate UC patients with rectal inflammation were randomly assigned either a 1 g mesalazine or placebo suppository. The suppository was administered in the rectum once daily for 4 weeks. The primary efficacy end point was the rate of endoscopic remission (mucosal score of 0 or 1) after 4 weeks.

Results
The endoscopic remission rates after 4 weeks in the mesalazine and placebo suppository groups were 81.5% and 29.7%, respectively, and the superiority of mesalazine to placebo was confirmed ($P < 0.0001$, chi-squared test). For proctitis, the endoscopic remission rates after 4 weeks were 83.8% and 36.1% in the mesalazine and placebo suppository groups, respectively, and the corresponding rates for all other types of UC were 78.6% and 21.4%, respectively. The superiority of mesalazine to placebo was confirmed in both subgroups ($P < 0.0001$, Fisher's exact test). The percentage of patients without bleeding was significantly higher in the mesalazine group than the placebo group from Day 3 of treatment ($P = 0.0001$, Fisher's exact test).

Conclusions
The effectiveness of mesalazine suppositories in all types of UC patients with rectal inflammation was confirmed for the first time in a double-blind, placebo-controlled, parallel-group study (JapicCTI- 111421).

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease. Its main symptoms are frequent defecation, bleeding and abdominal pain. These symptoms can lead to a decline in patient QOL. The disease is characterised by repeated episodes of active phases, where inflammation is present and symptoms are intense, and remission phases, where the inflammation and symptoms subside; and a complete cure is rare. Depending upon the extent of the lesions, UC is categorised as pancolitis, left-sided colitis, sigmoiditis, proctitis, etc. The treatments administered for UC include mesalazine preparations, adrenocorticosteroid preparations, and immunosuppressants, among which mesalazine preparations are widely used as standard treatment. For proctitis, mesalazine suppositories are recommended as the first-line drug for remission induction and maintenance of remission. In addition, oral mesalazine is widely used to treat left-sided colitis and pancolitis, though concomitant use with a topical mesalazine preparation is recommended.[1, 2]

Inflammation in UC has been reported to develop initially in the rectum and then spread more proximally over the course of time.[3–5] Even in patients who have an initial diagnosis of pancolitis, the rectal inflammation may be especially severe. Moreover, the rectum is said to be a site where inflammation tends to persist. In view of these observations, healing of the rectal area is extremely important in the treatment of UC regardless of the spread of lesions. Thus far, there have been numerous reports of the efficacy of mesalazine suppositories in UC patients with rectal inflammation.[6–11] In addition, mesalazine suppositories have been reported to act more rapidly and achieve significantly better results than oral mesalazine preparations.[12] While most of the patients in the preceding clinical studies on mesalazine suppositories had proctitis, in the American and European guidelines, coadministration of a topical mesalazine preparation with oral mesalazine was recommended even for pancolitis and left-sided colitis. We therefore decided to confirm the efficacy of mesalazine suppositories (Pentasa, Ferring Pharmaceuticals, Saint--Prex, Switzerland) in a double-blind, placebo-controlled study involving all types of UC patients with rectal inflammation, without limiting the study to those with proctitis. In addition, we categorised the subjects as having pancolitis, left-sided colitis, sigmoiditis or proctitis so that we could also investigate the efficacy of mesalazine suppositories (PentasaS) in each group.

METHODS

Protocol

This study was conducted in 45 Japanese medical institutions between March and October, 2011. It was conducted in conformity with the ethical principles of the Helsinki declaration, Good Clinical Practice and other relevant rules and regulations. Before beginning the study, we obtained the approval of the Institutional Review Board at each participating medical institution.

This study was a phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The mesalazine suppositories approved for use in Japan are salazosulfapyridine suppositories (SASP suppositories), but they have a different form from the mesalazine suppositories (Pentasa suppositories) used in this study. To conduct a double-blind comparative study with SASP suppositories as a control drug, we would have had to prepare the respective placeboes and insert two suppositories into the rectum each time. We thought that we could reduce the burden on the patients by using Pentasa suppositories as the placebo, because then only one suppository had to be administered each time. On the other hand, there was a 50% probability that any given patient would be assigned to the placebo group when a Pentasa suppository placebo was used as the control drug; so before the patients participated in this clinical trial, we provided all of them with a full explanation of the fact that this was a placebo-controlled study, and we had them give informed consent of their own free will in writing. If the patient was a minor, consent was obtained in writing from the patient as well as his/her legal representative. It was possible for the patient to withdraw from the clinical trial at any time if UC worsened, adverse events occurred, or the principal investigator judged continued participation in the trial to be inadvisable.

This study was registered with the Clinical Trials Registry (JapicCTI-111421).

Participants

The participants were to be men and women from 15 to 74 years old with UC. Additional inclusion criteria were rectal mucosal score of 2 or higher in the colonoscopic observation of the entire colon at the time of registration, UC-Disease Activity Index (UC-DAI)[13, 14] score between 4 and 8, and disease status of first attack or relapsing/remitting pattern. As the objective of this study was to confirm the efficacy of mesalazine in the rectal

inflammation for which the suppositories are indicated, patients with severe inflammation (colonic mucosal score of 2 or higher) in parts of the colon other than the rectum were excluded from the study so as to avoid drop-out of patients for reasons of worsening in that area before the intended evaluation could be performed. The details of the inclusion and exclusion criteria are given in Table 1.

Assignment

Patients were registered with a central registration system. The patients were randomly assigned to receive mesalazine or placebo suppositories at the start of study drug administration, according to a computer-generated randomisation scheme. Dynamic assignment was conducted using the rectal mucosal score (2 or 3), the disease pattern (relapsing/remitting or first attack), and the presence/absence of continuous administration of oral mesalazine or salazosulfapyridine as assignment factors.

Concomitant medication

Use of the following drugs and therapies was prohibited during the study: salazosulfapyridine preparations, mesalazine preparations, adrenocorticosteroid preparations, adrenocorticotropic hormone preparations, immunosuppressants, immunomodulators, metronidazole, ciprofloxacin, antidiarrhoeal agents, drugs for treating irritable bowel syndrome, surgical treatments for UC, cytapheresis and other drugs or therapies used for treating UC. However, in cases where the patient had been continuously using a salazosulfapyridine preparation in a dosage of 4500 mg/day or less, a mesalazine preparation in a dosage of 2400 mg/day or less, an herbal antidiarrhoeal preparation, or an irritable bowel syndrome treatment drug for 4 weeks or more at the start of study drug administration, continued use of the concomitant medication during the clinical trial period was allowed.

Study objective and end points

The purpose of this study was to verify the superiority of mesalazine suppositories over placebo suppositories in UC patients with mild-to-moderate symptoms and rectal inflammation at the time of registration who received one mesalazine (Pentasa, 1 g) or placebo suppository rectally once daily for 4 weeks. The primary efficacy end point was the endoscopic remission rate after 4 weeks of treatment (percentage of patients with rectal mucosal scores of 0 or 1 at the site of rectal inflammation

Table 1 | Inclusion and exclusion criteria

Inclusion criteria
Japanese patient aged 15–74 years with definitive diagnosis of UC
Patient in active phase at start of treatment with study drug (UC-DAI ≥4 and ≤8)
Rectal mucosal findings score of 2 or higher at start of treatment with study drug
Patient suffering initial attack or with relapsing/remitting type
Exclusion criteria
Patient with colonic mucosal score of 2 or higher for areas other than the rectum at start of treatment with study drug
Patient who has used a mesalazine preparation at a dosage exceeding 2400 mg daily or a salazosulfapyridine preparation at a dosage exceeding 4500 mg daily within 4 weeks prior to starting treatment with the study drug
Patient who has used an antidiarrhoeal agent or treatment drug for irritable bowel syndrome within 3 days prior to starting treatment with the study drug
Patient who has used a mesalazine enema, mesalazine suppository, or salazosulfapyridine suppository within 4 weeks prior to starting treatment with the study drug
Patient who has used an adrenocorticosteroid preparation (oral, enema, suppository, injection, or anal administration of ointment, etc.) within 4 weeks prior to starting treatment with the study drug
Patient who has started using a mesalazine preparation or salazosulfapyridine preparation or had a change in dosage and administration within 4 weeks prior to starting treatment with the study drug
Patient who has received cytapheresis within 4 weeks prior to starting treatment with the study drug
Patient who has used an immunosuppressant or immunomodulator (oral or injection) within 12 weeks prior to starting treatment with the study drug
Patient who has been treated with another investigational drug within 12 weeks prior to starting treatment with this study drug
Patient with a history of hypersensitivity to mesalazine preparations or salicylic acid–based drugs
Patient with a present or past history of serious kidney, liver, heart, lung, blood, or pancreatic disease
Patient with a malignant growth or a history of malignant growth within 5 years prior to starting treatment with the study drug
Patient who is pregnant, lactating, may be pregnant, or wishes to become pregnant during the study period
Patient who has been deemed unsuitable for participation in the clinical study by the principal investigator or a sub-investigator

observed at the time of registration). UC-DAI scores were used for a secondary evaluation of efficacy, and the secondary end points were the clinical remission rate after 4 weeks of treatment (percentage of patients with UC-DAI scores of 2 or less and a bleeding score of 0), the change in the UC-DAI score and the change in each item score. The safety end points were adverse events.

Evaluation

The study schedule called for the patients to come to the medical institution twice: at the start of study drug administration and after 4 weeks of treatment (or at the time of discontinuation). On each of these occasions, we made a UC-DAI assessment, including a colonoscopy, along with blood tests and measurements of vital signs. Evaluation of mucosal findings with a score of three without performing colonoscopy was allowed only in cases where performing this exam at the time of discontinuation was judged to be inadvisable because the patient's UC had worsened, the symptoms were markedly severe or it was judged necessary to begin remission induction therapy immediately after discontinuation. In addition, we checked for adverse events throughout the duration of the study. Symptom diaries were given to the patients to record symptoms of UC on a daily basis (number of bowel movements, bleeding status, severity of abdominal pain, stool appearance, desire to defecate, feeling of residual stool and impression of symptoms) as well as retention of the suppository in place.

Analysis

Efficacy was evaluated for all patients who received the study drug (ITT analysis). In addition, when colonoscopy was not performed at the time of discontinuation in a case where the patient withdrew from the trial for reasons other than worsening of UC, the case was regarded as not having reached remission induction in the calculation of the endoscopic remission induction rate. Superiority in terms of endoscopic remission rate was verified with the calculation of the endoscopic remission rate for each treatment group and then a between-group comparison using the Chi-squared test (without continuity correction). At the same time, the between-group difference (mesalazine vs. placebo suppositories) and its two-sided 95% confidence interval were calculated. The clinical remission rate was calculated for each treatment group and analysed using the Chi-squared test (without continuity correction). At the same time, the between-group difference (mesalazine vs. placebo suppositories) and its two-sided 95% confidence interval were calculated. For the change in the UC-DAI score, we totalled the frequency of each treatment group, calculated descriptive statistics, and performed a between-group comparison using analysis of covariance. For the change in each item score, we totalled the frequency of each treatment group, calculated descriptive statistics, and performed a between-group comparison using the van Elteren test.

A safety evaluation was performed in all patients who received the study drug. The frequency of occurrence for

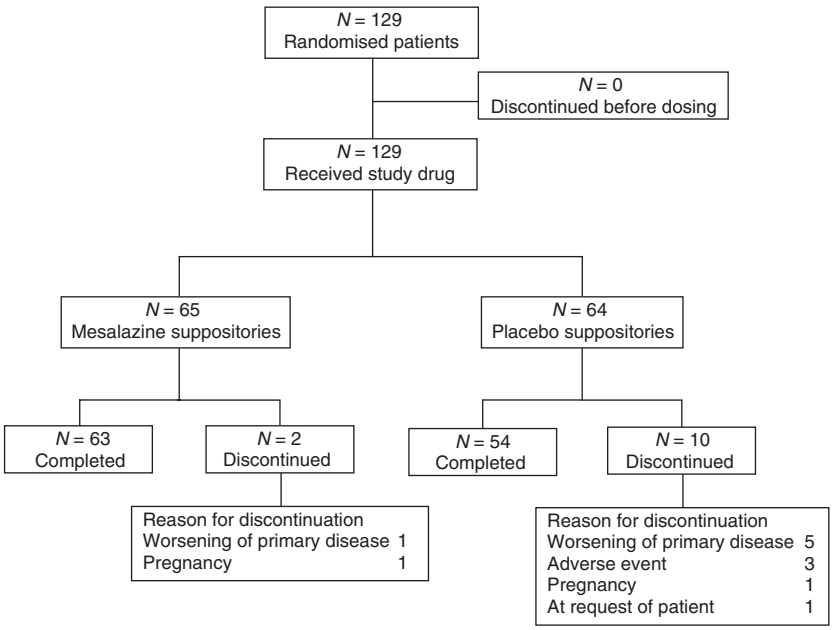

Figure 1 | Flow diagram of patients.

adverse events was totalled for each treatment group, and a comparison was performed using the exact test.

RESULTS

Flow of patients

A total of 129 patients were randomly assigned to the mesalazine suppository group (65 patients) or the placebo suppository group (64 patients) and 117 patients (63 and 54, respectively) completed the study (Figure 1).

Patient background

No significant difference between the groups was found for gender, age, height, weight, duration of UC, duration of the present active phase, clinical course, extent of lesions that have spread the most so far, presence/absence of complications, smoking habit (yes/no) or continuous administration of oral mesalazine, nor was there any between-group non-uniformity (Table 2).

Endoscopic remission rate and clinical remission rate

After 4 weeks of treatment, the endoscopic remission rates were 81.5% and 29.7% for the mesalazine and placebo suppository groups, respectively, with a significantly higher rate in the mesalazine group than placebo group (Table 3). After 4 weeks of treatment, the clinical remission rates were 63.1% and 17.2% for the mesalazine and placebo suppository groups, respectively, with a significantly higher rate in the mesalazine group than placebo group (Table 3). Moreover, in a subgroup analysis by category of pancolitis, left-sided colitis, sigmoiditis, or proctitis, both endoscopic and clinical remission rates

Table 2 | Background of patients

Characteristics	Mesalazine suppositories (N = 65)	Placebo suppositories (N = 64)	Test of non-uniformity
Gender			
Male, N (%)*	29 (44.6)	25 (39.1)	P = 0.5936†
Age (years), Mean (s.d.)	41.9 (12.2)	41.3 (12.5)	P = 0.7747‡
Height (cm), Mean (s.d.)	164.26 (8.52)	163.02 (8.45)	P = 0.4090‡
Weight (kg), Mean (s.d.)	59.1 (12.33)	57.64 (11.03)	P = 0.5020§
BMI (kg/m^2), Mean (s.d.)	21.79(3.53)	21.55 (2.86)	
Duration of UC (years), Mean (s.d.)	4.8 (6.1)	4.3 (4.9)	P = 0.9699§
Duration of present active phase (days), Mean (s.d.)	41.2 (56.6)	38.1 (39.2)	P = 0.7235§
Clinical course, N (%)			
First attack	19 (29.2)	17 (26.6)	P = 0.8448†
Relapsing/remitting	46 (70.8)	47 (73.4)	
Extent of past lesions, N (%)			
Pancolitis	11 (16.9)	7 (10.9)	P = 0.6364†
Left-sided	4 (6.2)	7 (10.9)	
Sigmoiditis	13 (20)	14 (21.9)	
Proctitis	37 (56.9)	36 (56.3)	
Complications, N (%)			
Yes	49 (75.4)	41 (64.1)	P = 0.1831†
Smoking, N (%)			
Yes	6 (9.2)	5 (7.8)	P = 1.0000†
Continued oral mesalazine, N (%)			
Yes	44 (67.7)	44 (68.8)	P = 1.0000†
Frequency score¶, Mean (s.d.)	1.1 (0.85)	0.8 (0.77)	
Bleeding score¶, Mean (s.d.)	1.6 (0.77)	1.6 (0.71)	
Mucosal score¶, Mean (s.d.)	2.1 (0.24)	2.0 (0.18)	
Investigator's global assessment¶, Mean (s.d.)	1.2 (0.50)	1.2 (0.43)	
UC-DAI¶, Mean (s.d.)	5.9 (1.39)	5.5 (1.27)	

* (%) = (Number of relevant patients/No. of patients in each group) × 100.

† Two-tailed significance level 15% (Fisher's exact test).

‡ Two-tailed significance level 15% (Student's t-test).

§ Two-tailed significance level 15% (Wilcoxon rank-sum test).

¶ Starting day of study drug administration.

Table 3 | Endoscopic remission and clinical remission after 4 weeks of treatment

	Mesalazine suppositories *N* (%)	Placebo suppositories *N* (%)	Between-group difference (%) [95% confidence interval]	*P*-value‡
Endoscopic remission*	53/65 (81.5)	19/64 (29.7)	51.9 [37.2, 66.5]	$P < 0.0001$
Clinical remission†	41/65 (63.1)	11/64 (17.2)	45.9 [31.0, 60.8]	$P < 0.0001$

* Patients with mucosal score of 0 or 1 after 4 weeks of treatment (or at time of discontinuation).

† Patients with UC-DAI of 2 or less and bleeding score of 0 after 4 weeks of treatment (or at time of discontinuation).

‡ Two-tailed level of significance 5% (χ^2-test).

after 4 weeks of treatment were higher with the mesalazine suppository group than the placebo suppository group in each of the subgroups (pancolitis, left-sided colitis, sigmoiditis and proctitis), and the difference was significant for all the groups except left-sided colitis (Table 4). Moreover, in the subgroups of pancolitis, left--sided colitis and sigmoiditis patients, both the endoscopic and clinical remission rates after 4 weeks of treatment were significantly higher for the mesalazine suppository group than placebo suppository group (Table 4).

UC-DAI and individual item scores

When the mesalazine suppository group and placebo suppository group were compared in terms of changes in UC-DAI and individual item scores after 4 weeks of treatment, the amount of change was significantly greater in the mesalazine suppository group in terms of the UC-DAI score as well as bleeding score, mucosal score and investigator's global assessment (physician's comprehensive assessment based on a survey of the abdominal discomfort accompanying UC; the patient's general condition; the physician's findings; and the patient's impressions of his/her own symptoms over the course of the 3 days of evaluation, excluding frequency score, bleeding score and mucosal score) (Table 5).

Bleeding elimination rate

A between-group comparison of the day-to-day change in the incidence of bleeding was made on the basis of the patients' symptom diaries. From Day 3 until the end of treatment, the percentage of patients without bleeding was significantly higher in the mesalazine suppository group than the placebo suppository group. Moreover, symptoms of bleeding disappeared in approximately 90% of patients in the mesalazine suppository group after 4 weeks of treatment (Figure 2).

Adverse events

The incidences of adverse events were 15.4% (10/65 patients) in the mesalazine suppository group and 17.2% (11/64 patients) in the placebo suppository group, with no significant between-group difference. The adverse event with a comparatively high incidence rate (2.0% or higher

Table 4 | Endoscopic remission and clinical remission in subgroups (pancolitis, left-sided colitis, sigmoiditis, proctitis, and all types other than proctitis) after 4 weeks of treatment

	Endoscopic remission* *N* (%)			Clinical remission† *N* (%)		
Type	Mesalazine	Placebo	*P*-value§	Mesalazine	Placebo	*P*-value§
Pancolitis	9/11 (81.8)	2/7 (28.6)	$P = 0.0491$	6/11 (54.5)	0/7 (0)	$P = 0.0377$
Left-sided	3/4 (75.0)	3/7 (42.9)	$P = 0.5455$	3/4 (75.0)	2/7 (28.6)	$P = 0.2424$
Sigmoiditis	10/13 (76.9)	1/14 (7.1)	$P = 0.0003$	7/13 (53.8)	1/14 (7.1)	$P = 0.0128$
Proctitis	31/37 (83.8)	13/36 (36.1)	$P < 0.0001$	25/37 (67.6)	8/36 (22.2)	$P = 0.0001$
Nonproctitis‡	22/28 (78.6)	6/28 (21.4)	$P < 0.0001$	16/28 (57.1)	3/28 (10.7)	$P = 0.0005$

* Patients with mucosal score of 0 or 1 after 4 weeks of treatment (or at time of discontinuation).

† Patients with UC-DAI of 2 or less and bleeding score of 0 after 4 weeks of treatment (or at time of discontinuation).

‡ Pancolitis, left-sided colitis and sigmoiditis.

§ Two-tailed level of significance 5% (Fisher's exact test).

Table 5 | Changes in UC-DAI, frequency score, bleeding score, mucosal findings score, and investigator's global assessment score, after 4 weeks of treatment

	UC-DAI		BM frequency score		Bleeding score		Mucosal score		Investigator's global assessment score	
Analysis group	Mesalazine	Placebo	Mesalazine	Placebo	Mesalazine	Placebo	Mesalazine	Placebo	Mesalazine	Placebo
ITT										
Number of patients	65	62	65	64	65	64	65	62	65	64
Change	−3.6	−0.9	−0.5	−0.1	−1.3	−0.3	−1.1	−0.3	−0.7	−0.1
s.d.	2.2	2.3	0.9	0.7	0.9	1.1	0.8	0.6	0.7	0.6
P-value	$P < 0.0001$ *		$P = 0.1094$ †		$P < 0.0001$ †		$P < 0.0001$†		$P < 0.0001$ †	
Proctitis										
Number of patients	37	35	37	36	37	36	37	35	37	36
Change	−3.5	−0.9	−0.3	−0.0	−1.3	−0.4	−1.2	−0.4	−0.7	−0.1
s.d.	2.0	2.3	0.7	0.6	0.8	1.2	0.7	0.7	0.7	0.7
P-value	$P < 0.0001$ *		$P = 0.3748$ †		$P < 0.0001$ †		$P < 0.0001$ †		$P = 0.0024$ †	
Nonproctitis										
Number of patients	28	27	28	28	28	28	28	27	28	28
Change	−3.7	−0.9	−0.8	−0.3	−1.3	−0.3	−1.0	−0.2	−0.7	−0.1
s.d.	2.5	2.2	0.9	0.8	1.0	0.9	0.8	0.5	0.7	0.6
P-value	$P = 0.0001$ *		$P = 0.0994$ †		$P = 0.0002$ †		$P = 0.0001$ †		$P = 0.0005$ †	
Pancolitis										
Number of patients	11	6	11	7	11	7	11	6	11	7
Change	−3.0	−1.7	−0.3	−0.3	−1.1	−0.4	−0.9	−0.5	−0.7	−0.3
s.d.	2.6	2.3	0.6	1.1	1.0	1.0	0.8	0.5	0.6	0.8
P-value	$P = 0.2481$ *		$P = 0.153$ †		$P = 0.0144$ †		$P = 0.1387$ †		$P = 0.0552$ †	
Left-sided										
Number of patients	4	7	4	7	4	7	4	7	4	7
Change	−4.0	−1.3	−1.0	−0.4	−1.3	−0.3	−1.0	−0.4	−0.8	−0.1
s.d.	2.3	2.1	0.8	0.5	1.3	1.1	0.8	0.5	1.0	0.7
P-value	$P = 0.0915$ *		$P = 0.3359$ †		$P = 0.2636$ †		$P = 0.2100$ †		$P = 0.3559$ †	
Sigmoiditis										
Number of patients	13	14	13	14	13	14	13	14	13	14
Change	−4.2	−0.3	−1.1	−0.2	−1.4	−0.1	−1.1	0.0	−0.7	0.1
s.d.	2.5	2.2	1.0	0.8	1.0	0.9	0.9	0.4	0.6	0.5
P-value	$P = 0.0021$ *		$P = 0.2691$ †		$P = 0.0020$ †		$P = 0.0005$ †		$P = 0.0059$ †	

* UC-DAI score: Analysis of covariance; two-tailed level of significance 5%.

† Other 4 scores: Van Elteren test; two-tailed level of significance 5%.

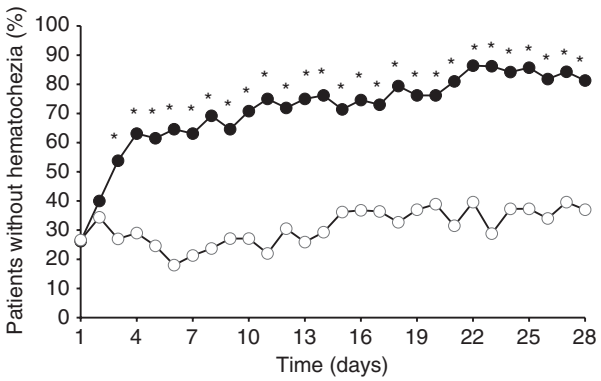

Figure 2 | Percentage of patients without bleeding, based on patient diaries. Mesalazine suppositories (●, $N = 65$), placebo suppositories (○, $N = 64$). * A statistically significant difference ($P < 0.0005$) was found between mesalazine suppositories and placebo (Fisher's exact test, two-tailed level of significance 5%).

in either group) was nasopharyngitis, with incidences of 7.7% (5/65 patients) and 6.3% (4/64 patients) in the mesalazine and placebo suppository groups, respectively (Table S1). No difference was found between the two groups in terms of type, severity or frequency of adverse events. Moreover, there were no serious adverse events.

DISCUSSION

This was the first study to evaluate the efficacy of mesalazine suppositories in UC patients presenting rectal inflammation, without limiting enrolment to patients with proctitis. After 4 weeks of treatment, mesalazine suppositories were confirmed to be effective in terms of both the endoscopic remission rate of the rectum and the clinical remission rate using the UC-DAI. On the basis of these results, mesalazine suppositories were confirmed to have a mucosal healing effect and improve clinical symptoms such as bleeding, abdominal pain and defecation urgency in UC patients with rectal inflammation.

A previous double-blind, placebo-controlled, comparative study by Campieri *et al.*[10] demonstrated the efficacy of mesalazine suppositories in 94 UC patients in which the range of inflammation was limited to an area less than 20 cm from the anus. After administering 1.0 g or 1.5 g mesalazine or placebo suppositories for 4 weeks, endoscopic remission (evaluated by Baron score) rates of 59%, 55% and 23%, respectively, were obtained with significantly higher rates for both the 1.0 g and 1.5 g mesalazine suppositories than for the placebo suppositories. The rates of clinical remission (no visible bleeding, bowel movements of less than 2 times/day and no other symptoms) were 69%, 74% and 39% for the 1.0 g and 1.5 g mesalazine and placebo suppositories, respectively, with significantly higher rates for the 1.0 g and 1.5 g mesalazine suppositories than for the placebo suppositories. Ngô *et al.*[11] demonstrated the efficacy of mesalazine suppositories in a double-blind, placebo-controlled, comparative study involving 50 patients with proctitis. After administering 1.0 g mesalazine or placebo suppositories for 2 weeks, endoscopic remission (Endoscopic Activity Scale = 0 or 1) was achieved in 69% and 33%, respectively, of patients, with significantly higher efficacy with the mesalazine suppositories than placebo suppositories. After 2 weeks of treatment, clinical remission (bowel movements of less than 3 times/day and no other symptoms) was achieved in 65% of the patients using mesalazine and 25% of those using the placebo, again showing higher efficacy with the mesalazine suppositories than the placebo.

In this study, the patients were categorised with pancolitis, left-sided colitis, sigmoiditis or proctitis, and the endoscopic remission rate and clinical remission rate were evaluated for each of the proctitis subgroup and nonproctitis subgroup. As a result, in the analysis for the proctitis subgroup and nonproctitis subgroup, patients treated with the mesalazine suppositories had significantly higher endoscopic and clinical remission rates than those who received the placebo, in both subgroups. On the basis of these results, it was reconfirmed that mesalazine suppositories are effective for UC with rectal inflammation.

At the same time, greater improvements in UC-DAI, frequency score, bleeding score, mucosal score and investigator's global assessment were obtained after 4 weeks of treatment with the mesalazine suppositories than with the placebo. Among these findings, the fact that the comparison of changes in individual item scores for the mesalazine suppository group showed large degrees of improvement in the mucosal score and bleeding score suggests that the mesalazine suppositories are highly effective in mucosal healing and improving bleeding. The high endoscopic remission rate after 4 weeks of treatment with the mesalazine suppositories also provides evidence of mucosal healing effect of the study drug. The change in bleeding over time based on the patients' symptom diaries confirms that the mesalazine suppositories had a significant effect from Day 3 of treatment onwards. In an open trial, comparing 1 g mesalazine suppositories with 100 mg of hydrocortisone foam in 242 patients with idiopathic proctitis, Lucidarme *et al.*[15] demonstrated the effectiveness of the mesalazine suppositories against bleeding. Specifically, symptom diaries

kept by patients using the mesalazine suppositories once daily for 14 days showed a decrease in the percentage of patients with bleeding from 85.6% at the time of entry to 43% on Day 2 of treatment and to 22.1% by Day 14. The results obtained in the present double-blind, placebo-controlled, comparative study support the results reported by Lucidarme *et al.*, and demonstrate that symptoms of bleeding were eliminated early on by mesalazine suppositories in UC patients with rectal inflammation. This suggests that mesalazine suppositories can contribute greatly to improving QOL by eliminating bleeding, which is one of the major symptoms of UC in the active phase.

Actually, while the number of pancolitis patients analysed as a subgroup was small, it was confirmed that mesalazine suppositories had a significant effect compared with the placebo, but in terms of the change in symptom score, no difference was observed in the frequency score, although a significant effect compared with placebo was confirmed for disappearance of bleeding.

It has been reported that inflammation in some UC patients starts in the rectum and then spreads over an extensive area of the colon over the course of repeated relapses and remissions.[3–5] Moreover, among patients with the relapsing/remitting type, the relapse often starts in the rectum and gradually expands in the oral direction.[3–5] Therefore, it is extremely important in the treatment for UC to quell rectal inflammation early on. This study did not include patients with severe inflammation in parts of the colon other than the rectum, but we think it was possible to prevent inflammation from spreading by providing reliable treatment for rectal inflammation. Moreover, the evaluation of adverse events has shown the mesalazine suppository to be a highly safe drug.

To summarize, these results reconfirm that mesalazine suppositories, which are highly effective against rectal inflammation, are an important drug in the treatment of UC. In the future, an investigation should be conducted to determine whether or not improvements in clinical symptoms would be obtained by administration of mesalazine suppositories in UC patients with extensive severe inflammation beyond the rectum.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Adverse events (AEs).

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