Effect of Weekend 5-Aminosalicylic Acid (Mesalazine) Enema as Maintenance Therapy for Ulcerative Colitis: Results from a Randomized Controlled Study

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Background: 5-Aminosalicylic acid (5-ASA) is known to be effective in the treatment of active ulcerative colitis (UC). The aim of the current study was to investigate the effect of 5-ASA enemas, as a maintenance therapy for UC, when administered twice weekly as a weekend treatment regimen, compared to daily oral 5-ASA alone. We hypothesized that the weekend enema therapy would be better tolerated by patients who worked or attended school.

Methods: Between January 2004 and August 2005, patients with UC, in whom remission of the condition had just been induced, were randomly assigned to either: the weekend 5-ASA enema group (n = 11), who received 1 g 5-ASA enemas twice a week on Saturday and Sunday plus oral 5-ASA 3 g/day for 7 days, or to the daily oral 5-ASA use only group (n = 13), who received only oral 5-ASA 3 g/day for 7 days. The primary endpoint of the study was defined as the incidence of relapse. The study was stopped after 24 patients had been enrolled because an interim analysis showed a significant benefit of the weekend 5-ASA enema group.

Results: In the weekend enema group, 2 patients (18.2%) had relapses compared with 10 (76.9%) in the oral 5-ASA only group. The multivariate hazard ratio of relapse associated with weekend 5-ASA enema, relative to the oral alone group, was 0.19 (95% confidence interval, 0.04–0.94).

Conclusions: This study demonstrated the beneficial effects of adding weekend 1 g 5-ASA enema to daily 3 g oral 5-ASA as maintenance therapy for UC.

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A curative therapy for ulcerative colitis (UC) has not been established. Both oral and topical (enemas or suppositories) 5-aminosalicylic acid (5-ASA) have been shown to be effective, either as monotherapy or in combination, for the treatment of active UC as well as for maintaining patients in remission.[1–13] However, although 5-ASA is effective and has an acceptable level of side effects, certain patients with active UC do not respond to it and require treatment with corticosteroids as a consequence.[14,15] Corticosteroid therapy, despite its efficacy, is frequently associated with less acceptable adverse effects than those associated with 5-ASA.[16] Thus, it is important to maintain remission of the disease as long as possible using the better-tolerated 5-ASA.

Four articles on randomized controlled trials (RCTs) have reported on the use of 5-ASA enemas as maintenance therapy and 2 of them investigated the intermittent use of 5-ASA enema.[1–4] Only 1 report indicated that intermittent use of 5-ASA enema combined with oral 5-ASA maintained remission better than oral 5-ASA only. D'Albasio et al[4] also reported an RCT in 72 patients with UC, in which oral 1.6 g 5-ASA combined with intermittent 4 g 5-ASA enema was more effective than oral 1.6 g 5-ASA alone. However, it would be reasonable to suppose that frequent enemas would not be well tolerated. We speculated that weekend enema therapy might be better tolerated compared to intermittent weekday enemas for patients who work or attend school.

For maintenance therapy, the optimal use of 5-ASA enemas remains to be determined. One limitation of the previous study concerns the dosage of 5-ASA (1.6 g 5-ASA orally and 4 g rectally) as the optimal rectal dose of 5-ASA, when given as a first-line treatment, has been established at 1 g/day.[9–13] In addition, Hanauer et al[17] reported that while the efficacy of oral 5-ASA was dose-related, there was no correlation between dose and the incidence of adverse events. Subsequently, the optimal oral dose 5-ASA has found to be

between 2 and 4 g. Another limitation of the study was that very few patients with the total colitis type of UC were included, and that the patients who had remained in remission for at least 3 months before beginning the study were included; in other words, these were patients with UC who were less likely to relapse. Therefore, a study with patients whose remission had just been induced would provide more reliable information because it would also include those who might easily relapse.

We report the results of a randomized controlled study that examined whether the addition of 1 g 5-ASA enema treatment twice a week, on Saturday and Sunday, to oral 5-ASA therapy (daily dose of 3 g) would have any additional benefit for UC patients in terms of maintaining remissions.

MATERIALS AND METHODS

Inclusion and Exclusion

Patients with UC were eligible for the study if they had just been induced into a phase of clinical remission. Exclusion criteria were: patients receiving oral maintenance treatment with sulfasalazine; severe renal/hepatic impairment; malignant disease; allergy to salicylates; alcoholism; drug addiction; any other disease or condition that might interfere with the study assessments; participation in another clinical study in the previous 30 days; women of child-bearing age who were not using an effective method of contraception; pregnancy; lactation; or established low compliance for 5-ASA enema, as judged by the investigator.

Patients

This randomized controlled study was conducted at 2 medical centers, Tohoku University Hospital and National Hospital Organization Sendai Medical Center, between January 2004 and August 2005. The diagnosis of UC, as well as the staging of activity, was established on the basis of standard clinical, endoscopic, and histological criteria.[18–20] Infectious colitis was excluded to confirm their fecal culture as normal flora. All subjects were outpatients attending the gastroenterological units of the 2 centers and presented with recent relapse of their disease prior to the study, which had been appropriately treated until clinical and endoscopic remission. The patients were invited to enroll without regard to the disease activity and their treatment prior to the induction of remission.

Remission was defined as the absence of symptoms and a score of less than 4 in the clinical activity index (CAI).[21–23] Briefly, the CAI score is the sum of 7 parameters, with 31 as the worst score: 1) weekly stool frequency (0, $<$18; 1, 18–35; 2, 36–60; 3, $>$60); 2) blood in stool (0, none; 2, little; 4, a lot, based on weekly average); 3) the investigator's global assessment of the symptomatic state (0, good; 1, average; 2, poor; 3, very poor); 4) abdominal pain/cramps (0, none; 1, mild; 2, moderate; 3, severe); 5) fever due to colitis (0, 37–38°C; 3, $>$38°C); 6) extraintestinal manifestations (3, iritis; 3, erythema nodosum; 3, arthritis); and 7) laboratory findings (1, sedimentation rate $>$50 mm in the first hour; 2, sedimentation rate $>$100 mm in the first hour; 4, hemoglobin $<$100 g/L).

The therapy to induce remission prior to enrollment in the study mainly consisted of oral 5-ASA and additional agents, including systemic medication (oral intake or intravenous injection) of corticosteroids (PSL, prednisolone), topical PSL, and 5-ASA enema. When systemic medication with PSL was used, treatment of active disease started at a daily dose of 40 mg oral PSL or a daily 60-mg intravenous injection; the dose of PSL was reduced 10 mg/day every 7 to 14 days according to the improvement of symptoms. In the case of PSL intravenous injection, the medication could be changed to an oral intake if their daily dose decreased to 40 mg or less. If their daily PSL dose became 20 mg, it was decreased 5 mg every 14 days. A requirement for enrollment in the study was a decrease of the daily dose of PSL to $\leq$20 mg. In the cases in which 60 mg PSL injection could not induce remission, cyclosporine A (CyA) was tried; the dose of CyA was 2–4 mg/kg/day for 14 days. In cases of topical PSL use, this had to cease in order for a patient to enroll, while in the case of 5-ASA enemas it was necessary to decrease the enema to twice a week or less. For all other treatments it was essential to stop the use of any additional drug(s) other than those described below. Antibiotics or any other type of enema were not permitted. Administration of immunosuppressive and antidiarrheal agents continued at the same doses as before relapse. In the case of induced remission by CyA, maintenance therapy of azathioprine (AZA) 50 mg/day was permitted. In all cases remission was evaluated between 1 week and 1 month after decreasing and/or stopping such medications. Patients fulfilling the entry criteria were enrolled within 1 month from the time of remission.

Randomization

Randomization was performed blind and independent of the 2 study centers by the Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine. The randomization cord was generated using a block size of 10. Patients were stratified by type of disease extension (I, total colitis type; II, left-sided colitis type; III, proctitis type) and clinical course (i, high relapse rate of 1 or more per year; ii, low relapse rate of less than 1 per year; iii, first attack). Stratification of the clinical course was based on data from a retrospective follow-up of patients with UC at Tohoku University Hospital, or reported previously from the other institutions, and was done according to the median duration of time in remission.

Eligible patients were randomly assigned to either the 5-ASA weekend enema or oral 5-ASA only groups. The former were to take a 1 g 5-ASA enema (Mesalazine; Pen-

tasa, Nisshin Kyorin Pharmaceutical, Tokyo, Japan) twice a week, on Saturday and Sunday, with 3 g oral 5-ASA (Mesalazine; Pentasa) tablets taken daily (i.e., Monday through Sunday). Patients in the oral 5-ASA only group were only to take 3 g oral 5-ASA daily.

Follow-up

Patients visited the study center for a follow-up assessment of the clinical course at least once every 3 months after randomization. In addition, they were advised to visit the study centers outside the 3-month visits if they had any symptoms. The clinical data were collected and blood tests for inflammatory parameters (erythrocyte sedimentation rate, C-reactive protein), full blood count, renal and liver function parameters, serum albumin, and electrolytes were performed at each follow-up visit. CAI evaluation was also done without endoscopic examination.

Usually, the endoscopic findings of inflammatory changes of colonic mucosa were evaluated by colonoscopy and graded as mild, moderate, or severe activity, while the absence of mucosal inflammatory changes was considered endoscopic remission according to the criteria of Baron et al.[19] In the clinical remission stage a colonoscopy was not performed. If clinical examinations suggested recurrence, disease activity was evaluated through colonoscopy.

Compliance was measured by obtaining a detailed study history during a personal interview as well as a review of the daily medication recorded on the diary cards themselves. Every participant was requested to complete these diary cards, which also included a performance report on CAI parameters.

Outcome Measures

The primary outcome measure was the incidence of relapse. Relapse was defined as a score of 6 or higher in CAI and more than 3 in the endoscopic index (EI).[21] Briefly, EI is the sum score of 4 parameters, with 12 as the worst score: 1) granulation scattering reflected light (0, no; 2, yes); 2) vascular pattern (0, normal; 1, faded/disturbed; 2, completely absent); 3) vulnerability of mucosa (0, none; 2, slightly increased (contact bleeding); 4, greatly increased (spontaneous bleeding)); and 4) mucosal damage (0, none; 2, slight; 4, pronounced, mucous, fibrin, exudates, erosions, ulcer). Even if the CAI score was lower than 6, the additional use of any medicine was considered a relapse since corticosteroids, antibiotic drugs, immunosuppressive agents, antidiarrhea agents, and also 5-ASA enemas more than twice a week could influence the activity of UC. Patients in whom the dose of corticosteroids could not be decreased were also considered as having relapsed.

Ethics

Written informed consent was obtained from each patient (or parent if the patient was <20 years of age) before enrollment in the study. Patients were free to withdraw from the study at any time during its course. The ethics committee at both study centers approved the protocol.

Statistical Analysis

Baseline characteristics were compared between the 2 groups using the χ^2 test and Student's *t*-test as appropriate. The unadjusted Kaplan–Meier curves for treatment in relation to the incidence of relapse were fitted. The Cox proportional-hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of relapse according to the treatment and to adjust for potentially confounding variables. We considered the following variables as potential confounders: age at baseline in years; sex and CAI score at baseline. For all models the proportional hazards assumptions were tested and met using time-dependent covariates. Analyses were performed using SAS v. 9.1 (SAS Institute, Cary, NC). A P-value <0.05 was considered statistically significant. Data were analyzed according to assignments regardless of their subsequent treatment (intent-to-treat analysis).

The study was designed and implemented by the steering committee in collaboration with the Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, who analyzed the data. The investigators wrote the article. The academic authors had access to the data and vouch for the validity and completeness of the data and the data analysis. A data safety and monitoring board reviewed the safety data with annual intermittent analysis. The investigation was designed to have a follow-up period of 2 years. Hypothesizing a minimal difference of 30% in the results obtained from 2 groups, and fixing the probability of α- and β-error <5%, for 90% power the number of patients required to be enrolled in each group was 100.

RESULTS

After the study had started, production problems led to a shortage in the supply of the enemas. Because of this recruitment was delayed and all patients were instructed and guided through the study by Tohoku University Hospital only, in close cooperation with the other hospital involved.

The annual interim analysis in January 31, 2005, indicated that the outcome was close to significance. At the suggestion of the safety monitoring board, a second interim analysis was performed 6 months later, on July 31, 2005. As this showed a significant difference between treatments, enrollment was stopped on August 17, 2005. The average observation period was 305 days (standard deviation 162).

Baseline Characteristics of Patients

Between January 2004 and August 2005, 72 patients were screened for inclusion in the study and of these 48 did not undergo randomization. The common reasons for exclu-

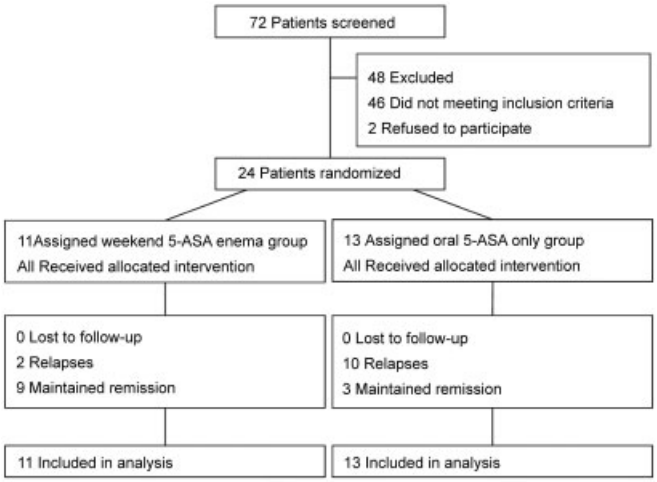

FIGURE 1. Flowchart of patient disposition.

sion were a shortage of enemas, lack of tolerance for the enema, a failure to induce remission, low dose of oral 5-ASA, and the need for contraindicated medication. Two eligible patients withdrew consent.

In total, 24 patients were randomized before the enrollment was stopped. Of these patients, 11 were allocated to the weekend 5-ASA enema group and 13 to the oral 5-ASA only group. The numbers of patients screened and randomized are shown in Figure 1; none withdrew during the study period. Patients in both treatment groups were comparable in age, sex, CAI score, extension, and clinical course of disease (Table 1); none had a history of surgery. There was no significant difference in terms of the induction therapy, CRP (C-reactive protein), ESR (erythrocyte sedimentation rate in the first hour), at enrollment (Table 2).

Primary Outcome

At the end of this study the proportion of patients in clinical remission differed significantly between the 2 treatment groups. Figure 2 shows the Kaplan–Meier estimates of the relapse rates for the 2 groups. In the group receiving weekend enemas combined with oral 5-ASA, 2 of 11 patients (18.2%) relapsed, compared with 10 of 13 (76.9%) in the group receiving oral 5-ASA alone (Table 2). The multivariate HR was 0.19 (95% CI, 0.04–0.94). We did not consider clinical course and extension type of UC as potential confounders. We could not perform stratified analysis due to the small number of patients.

Adverse Events and Tolerability

During the course of the study period none of the patients showed any adverse event related to the drugs apart from relapse of the disease. In the weekend enema group, 7 patients (63.6%), of whom 5 were still in remission and 2 had relapsed, stayed with the weekend enema regimen. Two patients (18.2%), both still in remission, switched to twice a week on weekdays. On the other hand, 2 patients (18.2%), both still in remission, stopped and/or changed the therapy.

TABLE 1. Patient Demographics and Characteristics at Entry into the Study

Baseline Characteristic	5-ASA Treatment Group: Weekend Enema Group (n = 11)	5-ASA Treatment Group: Oral Only Group (n = 13)	P-value
Gender			
Male	7	8	>0.999
Female	4	5	
Mean age (SD)	36.2 (11.88)	38.5 (13.91)	0.663
Clinical course			
High relapse rate	4	5	0.972
Low relapse rate	4	5	
First attack	3	3	
Extension type			
Total colitis	4	6	0.513
Left-sided colitis	7	6	
Proctitis	0	1	
Mean CAI (range)	0.50 (0–2)	0.42 (0–2)	0.326

CAI, clinical activity index; SD, standard deviation.

DISCUSSION

The results in this study indicated that weekend enema combined with oral 5-ASA maintained remission better than oral 5-ASA alone (multivariate HR, 0.19; 95% CI, 0.04–0.94). This is the first report in which the RCT was performed with the same dosage of 5-ASA (between 2 and 4 g oral, 1 g rectal) that is currently used worldwide.[9–13]

Although a previous RCT reported that intermittent 5-ASA enemas were effective as maintenance therapy for UC, the study protocols differed to a certain extent from that followed in the RCT reported here.[4] In particular, the dosage was different and patients who were prone to relapse were excluded from previous study due to a long observation period before enrollment. In contrast, the aim of this study was to dose the patients with 5-ASA according to present clinical practice (between 2 and 4 g oral, 1 g rectal) and also allowed for only a short observation period before the enrollment to avoid excluding patients prone to relapse. In addition, weekend enemas were administered in order to increase patients' compliance. Subsequently, this study demonstrated that the addition of weekend 5-ASA enema therapy to daily oral 5-ASA, significantly suppressed relapse. These results provide important information for clinicians. In the present study the oral 5-ASA only group showed a higher relapse rate

TABLE 2. Status of Patients in Detail

		5-ASA Treatment Group	
		Weekend Enema Group	Oral Only Group
Gender	Male	7	8
	Female	4	5
Mean age (SD)		36.2 (11.88)	38.5 (13.91)
Induction therapy			
	PSL	7	9
	5-ASA enema	3	4
	CyA	1	0
Mean follow-up period (SD)		251.7 (195.0)	349.7 (126.6)
Data at enrollment			
	Mean CAI (SD)	0.73 (0.95)	0.39 (0.77)
	Mean CRP (SD)	0.08 (0.09)	0.10 (0.92)
	Mean ESR (SD)	8.7 (10.13)	11.2 (9.56)
Outcome	Relapsed number	2	10
Data at the relapse			
	Mean CAI (SD)	7.5 (2.12)	5.2 (2.15)
	Mean EI (SD)	4.0 (0.00)	6.6 (2.50)
	Mean CRP (SD)	3.50 (4.67)	0.72 (0.82)
	Mean ESR (SD)	19.0 (21.2)	19.4 (27.2)
	Mean maintenance period (SD)	161.0 (130.1)	109.4 (103.0)

There was no significant difference except the outcome.
SD, standard deviation; CAI, clinical activity index; EI, endoscopic index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate in the first hour; PSL, prednisolone; CyA, cyclosporine A.

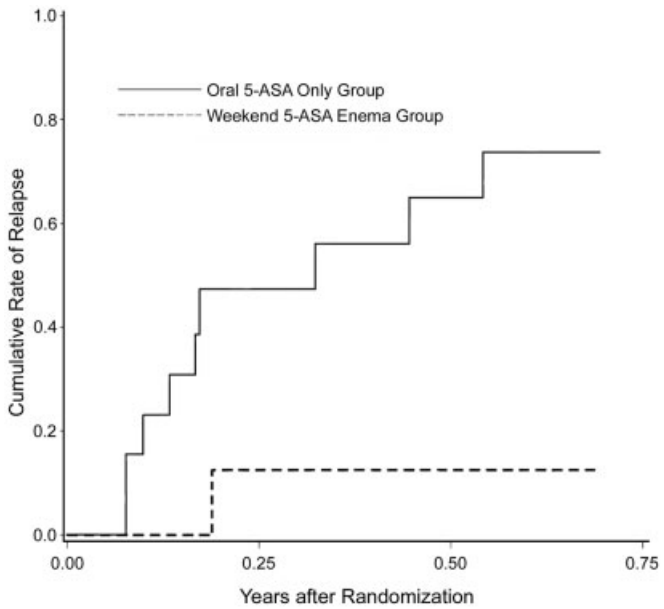

FIGURE 2. Kaplan–Meier cumulative event rates for both treatment groups.

than previous studies in spite of the high dose of oral 5-ASA used. This was possibly due to the fact that the present study enrolled patients who had just undergone the induction of remission. Nevertheless, we maintain that to obtain more reliable results it is important to examine patients who are likely to relapse easily.

The weekend enema combined with oral 5-ASA was well tolerated by the patients in the present study. However, the number of patients and the length of the observation period might have been insufficient for a definitive conclusion. Although the tolerability in previous studies was not described, we speculated that the weekend enema regimen might be better tolerated for patients who worked or attended school.

Another characteristic of this trial was that more patients with the total colitis type were enrolled compared to the 2 previous studies, in spite of the small number of patients with the proctitis type. Because 100 mL enemas do not generally spread beyond the splenic flexure, patients with UC extending above the splenic flexure require oral treatment. Although enemas cannot reach the entire colon, this type of treatment might nevertheless be effective for total colitis by maintaining the distal part of the colon, as the majority of

clinical symptoms in total colitis may relate to disease activity in this distal region.

The main limitation of this study was that it was a single-center, open-label, randomized controlled trial. A multicenter trial should be performed to exclude facility bias. Similarly, a double-blind study should be performed to exclude potential bias.

The second limitation was that only CAI evaluation was done, without endoscopic examination, for follow-up. We cannot exclude the possibility that 5-ASA enema controlled the symptoms of only the rectum to distal sigmoid colon. Because the purpose of this study was evaluation of a practical treatment, we did not perform endoscopic examination. As a practical measure in our facility, a colonoscopy is not usually performed in the clinical remission stage.

The third limitation was that we could not perform a stratified analysis due to the small number of patients. Further examination will be needed to confirm a tendency for each disease type.

A large number of patients with active UC underwent induction of remission in our facility, but most of them could not be enrolled within the observation period due to the shortage of 5-ASA enemas. Nevertheless, in spite of the smaller than planned number of patients, the primary endpoint indicated statistical significance. Although a type 2 error might have occurred due to the small number of patients, the steering committee judged the significance to repeat the interim analysis. They suggested discontinuation of the study because it was disadvantageous for patients to continue the study regardless of the significance.

Overall, the present study demonstrated the beneficial effects of adding 1 g 5-ASA weekend enemas to 3 g oral 5-ASA for maintenance therapy for UC. Despite the higher 5-ASA load of the oral/enema 5-ASA combination, no problems occurred with respect to the safety profile, and the combination treatment was well tolerated by the patients. In summary, weekend 5-ASA enema combined with oral 5-ASA could be a first-line maintenance treatment for UC.

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