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Efficacy of Long-Term 4.0 g/Day Mesalazine (Pentasa) for Maintenance Therapy in Ulcerative Colitis

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Background: High-dose (4.0 g/day) mesalazine is typically used for induction therapy, but its efficacy as maintenance therapy remains to be determined. We conducted a multicenter retrospective study to investigate the efficacy of continuous treatment with 4.0 g/day of mesalazine.


Material/Methods: Japanese ulcerative colitis (UC) patients receiving acute induction therapy with 4.0 g/day mesalazine were enrolled and followed. Those who clinically improved or who achieved clinical remission were categorized into 2 sub-groups according to the median duration of treatment with 4.0 g/day of mesalazine. The clinical relapse frequency and the time to relapse were analyzed.

Results: We enrolled 180 patients with active UC, and then 115 patients who clinically improved or who achieved clinical remission after treatment with 4.0 g/day mesalazine were categorized into 2 sub-groups according to the median of treatment duration: a short-term treatment group (≤ 105 days, $n=58$) and a long-term treatment group (>105 days, $n=57$). Overall, 45 (39.1%) patients relapsed: 28 (48.3%) in the short-term treatment group and 17 (29.8%) in the long-term treatment group. This difference was statistically significant ($p<0.05$). The relapse-free rate in the long-term treatment group was significantly higher than that in the short-term treatment group ($p<0.05$). The mean time to relapse in the long-term treatment group was significantly longer than that in the short-term treatment group (425.6 ± 243.8 days vs. 277.4 ± 224.5 days; $p<0.05$).

Conclusions: Long-term continuous treatment with high-dose mesalazine (4.0 g/day) may be more effective than short-term treatment for maintenance of remission in UC patients.

MeSH Keywords: **Colitis, Ulcerative – prevention & control • Colitis, Ulcerative – therapy • Mesalamine – administration & dosage**

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Background

Aminosalicylates are key drugs in the treatment of mild-to-moderate active ulcerative colitis (UC). Previous systematic reviews and meta-analyses have suggested that these drugs are effective in both inducing remission of mild-to-moderate active disease and in preventing relapse [1–3]. Mesalazine, a 5-aminosalicylic acid (5-ASA) compound, was developed as a better tolerated alternative to sulphasalazine and is now used throughout the world for the treatment of UC.

The efficacy of mesalazine in maintaining remission in patients with UC is well established [1–9]. Paoluzi et al. [5] demonstrated that patients taking 2.4 g of oral mesalazine remained in remission longer than those taking a 1.2 g dose. Fockens et al. [6] also demonstrated that a 3.0 g dose of oral mesalazine is more effective in the prevention of UC relapse than a 1.5 g dose. Miner et al. [7] demonstrated that a significantly greater number of patients maintained remission with a 4 g/day dose of mesalazine than with placebo, and the frequency of adverse events was not increased. Although Schroeder et al. [10] demonstrated that 4.8 g/day mesalazine is effective in inducing remission and in the short-term (6 weeks) for mildly to moderately active ulcerative colitis, the efficacy in the long-term for remission maintenance has not been demonstrated. The efficacy of high-dose (4.0 g/day) mesalazine as maintenance therapy remains to be determined. Therefore, we focused on the prevention of relapse in patients that showed improvement or achieved clinical remission, and conducted a multi-center retrospective study to investigate the efficacy of continuous treatment with 4.0 g/day mesalazine in patients with UC.

Material and Methods

Patients and data collection

We performed a retrospective cohort study. Japanese patients with UC were identified from 14 hospitals and 6 clinics associated with the Nagasaki IBD study group. Diagnosis was based on clinical, endoscopic, and histological features. From January 2008 to May 2012, patients who clinically improved or who achieved clinical remission after acute induction therapy with 4.0 g/day mesalazine were selected. Patients treated with concomitant azathioprine/6-mercaptopurine were excluded. The median duration of treatment with 4.0 g/day mesalazine (from date of initiation of 4.0 g/day mesalazine to the date to discontinuation of 4.0 g/day mesalazine, or from the date of initiation of 4.0 g/day mesalazine to September 1, 2012, if 4.0 g/day mesalazine was continued) was calculated. Patients were then categorized into 2 sub-groups according to the median duration of treatment with 4.0 g/day mesalazine: a short-term treatment group and a long-term treatment

group. Written consent was not sought for this retrospective study, as it did not affect the management of its subjects. However, patients who underwent continuous 4.0 g/day mesalazine therapy agreed to the treatment protocol. Approval for analysis of outcomes in this study was obtained from the Nagasaki IBD study group.

Data analysis

Data were obtained from medical records from January 2008 to September 2012. The clinical relapse frequency and the time to relapse from the date of initiation of 4.0 g/day mesalazine were compared between the 2 groups of patients. Relapse was defined as the occurrence of any clinical symptoms of UC requiring further rescue therapy. Fisher's exact test and Student's *t*-test were used to compare data from the 2 patient groups.

Survival times were evaluated using the Kaplan-Meier method, while the variability of these measurements was compared using the log-rank test. A *p*-value <0.05 was considered to indicate statistical significance.

Results

Of the 180 patients with active UC receiving acute induction therapy consisting of 4.0 g/day mesalazine, 139 showed clinical improvement or achieved clinical remission. Twenty-four patients treated with concomitant azathioprine/6-mercaptopurine were excluded. Median duration of treatment with 4.0 g/day mesalazine was 105 days. These 115 patients were then categorized into 2 sub-groups according to median treatment duration: a short-term treatment group (≤ 105 days, $n=58$) and a long-term treatment group (>105 days, $n=57$). The characteristics of the patients in the 2 groups at baseline are shown in Table 1. The mean exposure period to 4.0 g of mesalazine in the long-term and short-term treatment groups was 426 and 55 days, respectively. No significant differences were observed with regard to demographic or disease-specific parameters between the treatment groups.

Overall, 45 (39.1%) patients relapsed: 28 (48.3%) in the short-duration treatment group and 17 (29.8%) in the long-duration treatment group and this difference was statistically significant (Fisher's exact test, $p<0.05$) (Table 2). Median time to relapse from the date of initiation of 4.0 g of mesalazine was 266 days (range, 70–1088 days). The relapse-free rate, as determined by the Kaplan-Meier method, in the long-term treatment group was significantly higher than that in the short-term group (log-rank test, $p<0.05$; Figure 1). The mean number of days from the date of initiation of 4.0 g of mesalazine to the date of relapse in the long-term treatment group was significantly longer than that in the short-term treatment group (425.6 ± 243.8 days vs. 277.4 ± 224.5 days; Student's *t*-test, $p<0.05$) (Table 2).

Table 1. Baseline characteristics of study population.

Features	Short-duration treatment group (≤105 days, n=58)	Long-duration treatment group (> 105 days, n=57)	p-value
Exposure period (mean ±SD)	54.5±25.6	425.7±267.7	N.S.
Sex – female/male	32/26	30/27	N.S.
Age (years)			
Median	46	40	N.S.
Range	14–84	18–81	N.S.
Disease			
Duration (years)			
<10	41	40	N.S.
≥10	17	17	N.S.
Extent			
Total	35	27	N.S.
Left-sided	20	25	N.S.
Proctitis	3	5	N.S.

Table 2. Relapse rate and time to relapse in long-term treatment group and short-term treatment group.

Patients groups	N	Relapse n (%)	Time to relapse mean ±SD
Long-duration treatment (>105 days)	57	17 (29.8)*	425.6±243.8*
Short-duration treatment (≤105 days)	58	28 (48.3)*	277.4±224.5
Total	115	45 (39.1)	333.4±240.5

*p< 0.05

The following adverse effects were reported in 1 patient each among the 180 treated patients: diarrhea, dyspnea, liver dysfunction, and drug-induced lupus.

Discussion

The European Crohn’s and Colitis Organisation stated that the minimal effective dose of oral 5-ASA for remission maintenance of patients with UC is approximately 1 g/day [1]. The current guidelines of the Japanese Ministry of Health, Labour and Welfare suggest low-dose mesalazine (1.5–2.25 g/day) as maintenance therapy for patients with UC [11]. A dose of 4.0 g/day is significantly superior to 2.25 g/day in inducing remission or improvement of active UC [12]. After patients have achieved remission or have improved with 4.0 g/day mesalazine, the dose is reduced to 1.5–2.25 g/day. However, even when receiving treatment with low-dose mesalazine, a quarter

of patients with quiescent UC relapse within a year [13]. It is possible that some patients require high doses of mesalazine for maintenance therapy, although there is no good evidence to support this [14]. Therefore, we conducted this study to investigate the efficacy of continuous treatment with 4.0 g/day of mesalazine in patients that improved or achieved clinical remission when treated with 4.0 g/day of mesalazine. To our knowledge, this is the first study in Japan to evaluate the effects of high-dose mesalazine (4.0 g/day) for maintenance therapy in patients with UC. In this retrospective study, we showed that long-term treatment with high-dose mesalazine (4.0 g/day) was more effective than short-term treatment for prevention of relapse in UC patients.

The therapeutic effects of 5-ASA depend on direct contact with the colonic mucosa. Naganuma et al. [15] demonstrated an inverse correlation between rectal mucosal concentration of 5-ASA and disease activity levels in UC, speculating that a high mucosal

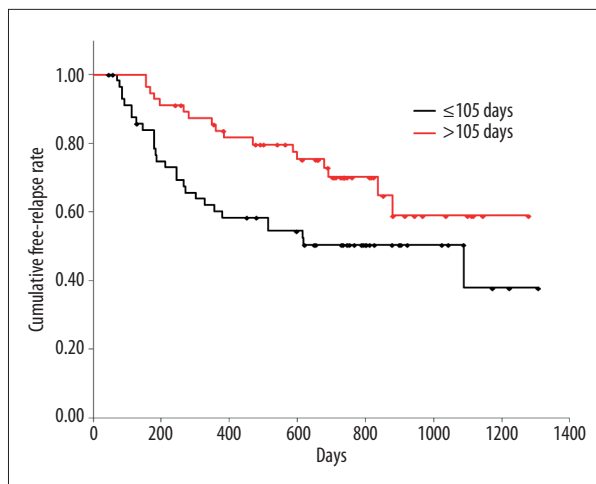


Figure 1. Kaplan-Meier plot showing cumulative relapse-free rate in relation to time after treatment with 4.0 g/day mesalazine.

5-ASA concentration is an accurate predictor of good therapeutic effect in patients with UC. Frieri et al. [16] reported that a high ileac mucosal concentration of 5-ASA is necessary for the prevention of postoperative relapse in patients with Crohn's disease. Therefore, maintenance of remission in patients with UC might also depend on the colonic mucosal concentration of 5-ASA.

Very recently, Khan et al. [17] demonstrated that there were no significant differences in long-term relapse risk when comparing low- and high-dose mesalazine therapy, as long as the patients maintained a high-to-moderate level of adherence to the therapeutic regimen. This suggests that adherence is more important than daily dose. In the present study, because we did not simultaneously obtain therapy adherence data in our subjects, we were unable to analyze the combined effect of dose and adherence rates on remission maintenance. Travis et al. [18] demonstrated that patients in remission for <12 months required a high dose of olsalazine (2 g/day) to prevent relapse, and the drug dose was less important for those already in longer-term remission (>2 years). This further suggests that a higher luminal concentration of 5-ASA may be necessary in the early stages of remission. In the present study, the mean time to relapse in the short-term treatment group was 282.9 ± 217.2 days, and most relapses occurred within 12 months of the start of acute induction therapy. Although good adherence may be more important than high mucosal concentrations of 5-ASA for long-term maintenance of remission [17], high-dose mesalazine (4.0 g/day) may be necessary in the early stages of remission maintenance.

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Safety and tolerance are important aspects of chronic maintenance treatment. In this analysis, 4.0 g/day mesalazine was well tolerated. No unexpected adverse events were observed. Most reported drug-related intolerance occurs early in treatment [7].

Conclusions

In conclusion, the results emerging from the present study showed that long-term continuous treatment with high-dose mesalazine (4.0 g/day) may be more effective than short-term treatment for maintenance of remission in UC patients. The investigators acknowledge that this study has several limitations. First, the retrospective and nonrandomized nature of the design entailed an inherent bias in patient selection and confounding. Second, our population included only patients who clinically improved or who achieved clinical remission. Therefore, this population may have consisted of patients who had not achieved full mucosal healing, as well as those who had achieved complete clinical and endoscopic remission. To confirm our findings, prospective randomized controlled trials are necessary.

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