Timing for dose-down of 5-ASA depends on mucosal status with ulcerative colitis

Short title: Dose-down of 5-ASA in UC

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ABSTRACT

Objective

Although aminosalicylic acid (ASA) preparations have been used as first-line drugs for the treatment of Ulcerative colitis (UC), no consistent view has been established regarding the ASA dose during the remission-maintenance phase of the disease. In this study, we examined whether the ASA dose should be reduced during the remission-maintenance phase.

Materials and methods

This study included 203 patients in the remission-maintenance phase of UC. The Mayo endoscopic subscore (MES) was used to evaluate mucosa. Comparison and analysis were performed between patients whose ASA dose had been unchanged and whose dose had been reduced, between patients with endoscopic healing (EH) group and those without endoscopic healing (WEH) group, and between patients with an MES of 0 and 1.

Results

Comparison between the unchanged-ASA and reduced-ASA groups revealed that the remission-maintenance rate was higher in the unchanged-ASA group ($P < 0.001$). Next, the remission-maintenance rate was higher in the EH/unchanged-ASA group than in the EH/reduced-ASA group ($P = 0.042$).

Comparison between the MES 0 and MES 1 groups revealed that the remission-maintenance rate was higher in the MES 0 group (P = 0.007).In addition, no significant difference in remission-maintenance rates was observed between the MES 0/unchanged-ASA group and the MES 0/reduced-ASA group (P = 0.108).

Conclusions

When the same ASA dose is maintained regardless of the presence or absence of EH, remission is more likely to be maintained. If the ASA dose must be reduced, dose reduction is more advantageous after an MES of 0 is achieved.

Keywords: ulcerative colitis, aminosalicylic acid, endoscopic healing, clinical remission

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology that is localized to colonic mucosa. The disease manifests with clinical symptoms such as abdominal pain, diarrhea, and bloody stool, and is characterized by a cycle of relapse and remission. While no fundamental therapeutic strategy has been established, the therapeutic goals are to achieve remission by suppressing symptoms such as abdominal pain and bloody stool, and to maintain remission [1].

Aminosalicylic acid (ASA) preparations are thought to act on colonic mucosa and to suppress inflammation in UC. These preparations have been used for the treatment of UC for a long period [2]. Several previous studies have shown that in patients with mild-to-moderate UC, remission-induction and remission-maintenance rates were higher in those patients receiving ASA than in those patients receiving placebo. Unlike corticosteroids and immunomodulators (IMs), the difference in the incidence of adverse reactions was not significant between the ASA and placebo groups, and ASA is used as a first-line drug for the treatment of UC [3-5]. Previous studies have shown that remission-maintenance rates are higher with higher ASA doses and better adherence [6]. However, high oral doses lead to poor adherence in patients, and long-term treatment with a

high dose increases medical costs. So, reductions in ASA dose need be considered possible. However, at present, there has been no consistent view on the criteria for reduction of the ASA dose.

In recent years, studies have shown that achievement of mucosal healing (MH) in patients with UC leads to reduced rates of relapse and hospitalization, as well as fewer surgeries for colorectal cancer and other conditions [7-9]. A view that therapeutic goals should be set for achieving not only clinical remission but also MH has been widely accepted [10]. However, no consistent view has been established regarding ASA doses after achievement of MH.

In this study, we retrospectively investigated whether ASA doses could be reduced in patients with UC in the remission-maintenance phase. We also examined whether endoscopic healing (EH) could serve as a rationale for reduction of ASA dose.

MATERIALS AND METHOD

Patients

This study targeted patients with UC who have maintained remission for at least one year with 5-ASA alone or combination use of 5-ASA and IM, had undergone

colonoscopy of the mucosa, and had showed good adherence (defined as taking 80% of prescribed doses according to medical records) during regular visits to Dokkyo Medical University Hospital or Japanese Red Cross Ashikaga Hospital between January 2008 and December 2014. Among patients concomitantly receiving IM, those receiving IM at a constant dose during the follow-up period were included. Clinical remission was defined as a clinical activity index (CAI) [11] of 4 or below. The scores of CAI were retrospectively calculated, based on the data drawn from the medical records. We selected 207 patients who received a constant dose of ASA for at least one year or whose ASA dosage was reduced during this follow-up period for the study.

An ASA dose of 3600 mg or more per day in mesalazine equivalent was considered a high dose, and that less than this dose was regarded as a low dose. Specifically, the high dose was 4000 mg per day of time-dependent ASA (Pentasa®, Kyorin Pharmaceutical Co., Ltd) and 3600 mg per day of pH-dependent ASA (Asacol®, Zeria Pharmaceutical Co., Ltd.). In patients receiving salazosulfapyridine (Salazopyrin®, Pfizer Japan Inc.), all doses were considered low doses because the salazosulfapyridine doses expressed in ASA equivalent were lower than the doses of the two drugs described above. Dose reduction of 5-ASA was considered for patients who had been in clinical remission for at least one year based on

endoscopic findings.

This study has been approved by the ethics committee of Dokkyo Medical University.

Endoscopic findings and endoscopic healing

The Mayo endoscopic subscore (MES) [12] was used for endoscopic evaluation of mucosa, and an MES of 0 or 1 was considered to indicate EH. Endoscopic findings were evaluated by three endoscopists specialized in the treatment of inflammatory bowel disease. The images on the display of the computer were viewed by endoscopists who were blinded to the clinical data, and scores agreed upon by at least two of the endoscopists were used for analysis. Scores obtained from the sections of the large intestine (the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) with the most severe inflammation were used. Thus, endoscopic assessment was based on validation of endoscopic pictures. After four patients with multiple sections of large intestine scored as MES 1 and 2 were excluded, a total of 203 patients were considered to be eligible for analysis. Table I shows characteristics of these patients. The majority of patients had pancolitis type. There were 176 patients whose mucosa was evaluated as MES 0 or 1.

Moreover, in order to investigate whether differences existed between patients with an MES of 0 and an MES of 1, we selected patients whose mucosa was evaluated as MES 0 or 1 by all three endoscopists. Of the 176 patients, 120 were assigned the same score by the endoscopists. These patients included 96 patients with an MES of 0 and 24 patients with an MES of 1 (Figure 1). These patient groups were then compared and analyzed.

Data analysis

First, the patients were divided into two groups for comparison and analysis: those whose ASA dose remained unchanged and those whose ASA dose was reduced. Next, the patients were divided into those with or without EH for comparison and analysis. Furthermore, the patients with EH were divided into those with MES 0 or 1 for comparison and analysis. In addition, age, sex, disease duration, lesion range, concomitant use of IM, and history of hospitalization were also analyzed to investigate whether there were risk factors likely to cause relapse.

Statistical analysis

Statistical analysis was performed with statistics software (IBM SPSS Statistics

21®, IBM Japan, Ltd.). For comparison of remission-maintenance rates, survival curves were generated by Kaplan-Meier method and log-rank test was performed. Student's *t* test was used to analyze age and disease duration. While the χ^2 test was used for comparison by sex, use of IM, and history of hospitalization, Fisher's exact test was used for variables with an expected value of 5 or less. A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULT

Comparison with continuation and reduction of the ASA dose

Patient characteristics in the unchanged-ASA and reduced-ASA groups are shown in Table II. First, comparison and analysis between these groups revealed that the remission-maintenance rate was statistically significantly higher in the unchanged-ASA group ($P < 0.001$) (Figure 2). Then, after the unchanged-ASA group was divided into patients receiving the high dose of ASA (HD group) and those receiving the low dose of ASA (LD group) for analysis, the remission-maintenance rate was significantly higher in the LD group, as compared with that in the reduced-ASA group ($P < 0.001$). The HD group showed higher remission-maintenance rates than the reduced-ASA group, but the

difference did not reach statistical significance ($P = 0.092$) (Figure 3).

Relationship of endoscopic healing and ASA dose

The unchanged-ASA and reduced-ASA groups were combined and then divided into patients with EH group and those without endoscopic healing (WEH) group for analysis. The EH group included 176 patients, and the WEH group included 29 patients. These groups were compared and analyzed. The EH group showed significantly higher remission-maintenance rates, as compared to the WEH group ($P = 0.020$) (Figure 4). When the unchanged-ASA and reduced-ASA groups were separately divided into 4 groups according to EH status for analysis, a significant difference in the remission-maintenance rates was observed between the EH/unchanged-ASA group and the EH/reduced-ASA group ($P = 0.042$) (Figure 5). Meanwhile, when the EH/unchanged-ASA group and the WEH/unchanged-ASA group were compared, no significant difference was observed in the remission-maintenance rates ($P = 0.245$). The WEH/reduced-ASA group included only 4 patients, all of whom experienced relapse.

Comparison with MES 0 and MES 1

The patients with an MES of 0 or 1 were analyzed for remission rates. The

patient characteristics of the MES 0 and MES 1 groups are shown in Table III. When we examined whether the remission-maintenance rates differed between these groups, a statistically significant difference was observed (P = 0.007). Furthermore, each of these groups was divided by ASA dose, and the resulting four groups were analyzed (Figure 6). No statistically significant difference was observed between the MES 0/unchanged-ASA and MES 1/unchanged- ASA groups (P = 0.108). Moreover, comparison between the MES 0/unchanged-ASA and MES 0/reduced- ASA group did not show any statistically significant difference (P = 0.111). The MES 1/reduced-ASA group included only 4 patients, half of whom experienced relapse during the follow-up period.

Risk factor

Patients with EH or MES 0 were divided into two groups according to the presence or absence of relapse for comparison. No difference was observed in age, sex, disease duration, lesion range, presence or absence of concomitant use of IM, or presence or absence of history of hospitalization.

DISCUSSION

Earlier studies have shown that in the treatment of mildly or moderately active UC, high ASA doses led to higher rates of inducing remission or achieving EH, compared to low doses [12-15]. However, there has been no consistent view on the determination of ASA doses for UC in the remission-maintenance phase.

Our study showed that relapse rates were higher in patients with UC in the remission-maintenance phase whose ASA dose had been reduced than in those whose ASA dose had remained unchanged, suggesting that ASA dose should not be reduced on the basis of only clinical remission. Regarding the reasons for the higher remission-maintenance rates in the LD group than in HD group, we speculate that there may have been a selection bias that caused the HD group to include more patients with initial highly active disease, resulting in more patients consequently experienced relapse in the HD group.

Moreover, in recent years, EH has been recommended as a goal in the treatment of UC. In a workshop of the European Crohn's and Colitis Organization (ECCO), EH was indicated to be helpful [16]. This is mainly attributed to earlier studies showing that EH reduces the incidence rate of colorectal cancer [7-9], relapse rate [17,18], and the like. Particularly, histological stimulation due to severe inflammation or chronic persistent inflammation has been implicated as a major risk factor for the development of colorectal cancer [7,19].

According to an article summarizing the ASCEND (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA) I and II trials, comparison between patients with moderately active UC who received pH-dependent ASA at a dose of 4.8 g per day and those who received the drug at a dose of 2.4 g per day revealed that the proportion of patients achieving EH after 6 weeks of treatment was higher in the former [20]. In patients with mildly active UC, the proportion of those achieving EH was high in either dose, showing no significant difference. In consideration of these findings together with our results, we recommend high ASA doses to achieve EH.

Regarding the association between EH and ASA doses, as with an earlier study [10], our study also revealed that the remission-maintenance rate was significantly higher in the EH group. However, the rate in the EH/reduced-ASA group was significantly lower than that in the EH/unchanged-ASA group. Although the WEH/reduced-ASA group included only 4 patients, relapse was observed in all of them. Thus, it seems that ASA doses should not be reduced when EH is not observed. When comparing the EH/unchanged-ASA and WEH/unchanged-ASA groups, no significant difference was observed in remission-maintenance rates. This indicated that remission could be maintained by keeping ASA doses unchanged even in patients WEH. According to these

results, when an MES of 0 or 1 is considered to indicate EH, reduction of ASA dose may not be recommended even in patients with EH.

While EH is defined as an MES of 0 or as an MES of 0 or 1 in previous studies [13,17,21], we defined EH as an MES of 0 or 1 in our study. Comparing patients with an MES of 0 and an MES of 1, Meucci et al [17]reported no difference in remission-maintenance rates, whereas Nakarai et al [22] reported that the rates were significantly higher in patients with MES 0 in agreement with our study. The disagreement between the results of these studies may be attributable to differences in study designs. The study conducted by Meucci et al included only patients who achieved clinical remission after 6 weeks of consecutive administration of 4 g of oral mesalazine and 2 g of transanal mesalazine, and these patients were prospectively followed for up to one year. On the other hand, the study conducted by Nakarai et al is a retrospective study with 6 years of follow-up that had no exclusion criteria regarding treatments for patients. Moreover, our study included only four patients with an MES of 1 who received reduced ASA dosage, and two of them experienced relapse. These results indicate that there is a difference between conditions evaluated as MES 0 or MES 1, which are frequently considered to indicate EH. It is assumed that ASA doses should be reduced after MES is lowered to 0. In addition, a previous study has shown that

patients with an MES of 0 account for approximately 55% of patients with clinical remission, while the remaining 45% have inflammatory mucosa evaluated as MES 1 or above [23]. Endoscopic evaluation may be required as needed.

In recommending EH as a therapeutic goal, the lack of an established definition of EH is a problem. Although there are currently many studies in which an MES of 0 or 1 are considered to indicate EH, our study revealed a difference in relapse rates between patients with MES 0 and MES 1. So, it is required that specific standards will be established for the term of EH in the future.

In this study, we investigated risk factors for relapse in patients with UC, considering the presence of a history of hospitalization to be an indication that a patient had experienced severe relapse. As a result, none of the variables that we analyzed was identified as a risk factor for causing relapse.

This study has the following limitations: First, because the severity of inflammation in the active phase and the methods used to induce remission were not determined, this study might have included patients who were more likely to experience relapse. Second, time-dependent ASA, pH-dependent ASA, and salazosulfapyridine were all considered the same treatment. A study conducted by Ito et al showed that pH-dependent ASA is significantly more effective on proctitis-type UC than time-dependent ASA [24]. However, the differences in the

effects of different types of ASA were not taken into consideration in our study. Third, the presence or absence of concomitant local treatment was not included in the criteria. Marteau et al has shown that, in mild to moderate UC including but not limited to proctitis-type UC, remission-induction rates were higher after treatment with a combination of oral ASA and suppository than after treatment with oral ASA alone [25,26]. In our study, the differences in remission-maintenance rates may have been caused by the presence or absence of concomitant use of drugs. Fourth, our study is a single-center retrospective study with a small sample size. The number of patients is not large enough to allow statistical analysis. For example, there were only four patients WEH whose dose was reduced.

In conclusion, our study has shown that even in patients with clinical remission or EH, relapse was more likely to be prevented by keeping ASA doses unchanged than by reducing them. Thus, we recommend keeping the dosage unchanged as much as possible. The results of this study also raise the possibility of a difference in remission maintenance rates between patients with MES 0 and those with MES 1, suggesting that achievement of MES 0 could be a useful treatment goal. In the future, this issue, as well as possible risk(s) of relapse, should be investigated in multicenter, prospective studies.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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FIGURE LEGENDS

Figure 1. Flow chart to identify patients eligible for analyses.

Figure 2. Comparison between the unchanged-ASA and reduced-ASA groups revealed a significant difference in remission-maintenance rates ($P < 0.001$).

Figure 3. Comparison between the low dose of ASA (LD) and reduced-ASA groups revealed a significant difference in remission-maintenance rates ($P < 0.001$).

Figure 4. Comparison between the endoscopic healing (EH) and without endoscopic healing (WEH) groups revealed a significant difference in remission-maintenance rates ($P = 0.020$).

Figure 5. Comparison between the endoscopic healing (EH) / unchanged-ASA and the EH / reduced-ASA groups revealed a significant difference in remission-maintenance rates ($P = 0.042$).

Figure 6. Comparison between the Mayo endoscopic subscore (MES) 0/unchanged-ASA and MES 0/reduced- ASA groups revealed no significant difference in remission-maintenance rates ($P = 0.111$).