Efficacy of Pentasa Tablets for the Treatment of Inflammatory Bowel Disease

Jau-Min Wong and Shu-Chen Wei

Background and Purpose: The Eudragit S formulation of delayed-release 5-aminosalicylic acid (5-ASA), Asacol® tablets (AT), has limited efficacy in maintaining remission in patients with inflammatory bowel disease (IBD). This study evaluated the effect of switching patients with unsatisfactory results under treatment with AT to a microgranule delayed-release formulation of 5-ASA, Pentasa® tablets (PT).

Patients and Methods: A 12-week, open drug-switching study was conducted in 15 IBD patients, including 9 with ulcerative colitis (UC) and 6 with Crohn's disease (CD) who were evaluated at the time of switching from routine AT (2.4 g/day) treatment (for more than 3 months) to PT (4 g/day). UC patients were those under AT remission maintenance and they were defined as prone-to-relapse because of endoscopy scores ≥ 2. CD patients were those under acute treatment with AT who had not attained a complete remission. The primary endpoint was the change in UC Disease Activity Index (UC-DAI) or the CD Activity Index scores after switching to PT therapy. Drug safety profile and patient acceptability were secondary endpoints.

Results: Twelve weeks after switching to PT treatment, the mean (± SEM) UC-DAI score was reduced significantly, from 8.18 ± 0.58 to 6.81 ± 0.72 ($p = 0.013$) in UC patients. Subcategory scores indicated improvements in endoscopy scores and in physician global assessment. Though the change in clinical outcomes did not reach significance for CD patients, a trend towards a therapeutic benefit was observed. No adverse event was observed during the 12-week clinical trial.

Conclusion: PT may provide a better alternative for IBD patients with unsatisfactory response to AT therapy.

Key words: Aminosalicylic acids; Comparative study; Delayed-action preparations; Inflammatory bowel diseases; Mesalamine

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Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is an uncommon disease in Asia. In Taiwan, IBD patients represent only a tiny proportion of the Taiwanese population (around 1000 patients in Taiwan which has a population of 23 millon people). Most of these patients suffer from chronic UC. However, there is a recent rising trend of IBD incidence in Taiwan.

IBD is still a non-curable disease. Most patients attain remission by medical means, typically through treatment with 5-aminosalicylic acid (5-ASA). Characteristically, disease relapse occurs a certain time after drug withdrawal. Hence, IBD patients in remission are routinely prescribed maintenance doses of 5-ASA. Asacol® tablets (AT), a proprietary brand of 5-ASA, given at a dose of 1.2 to 2.4 g/day is a standard maintenance therapy for IBD patients in our clinic.

AT is a simple delayed-release formulation of 5-ASA for IBD treatment. 5-ASA in AT is coated with a thin layer of acrylic-based resin known as Eudragit S. This coating is resistant to the low pH conditions of the stomach, but it dissolves rapidly when the pH is greater than 7.[1] After the coating is removed, 5-ASA is released instantaneously. This kind of design creates several clinical disadvantages in vivo, such as dose dumping, pH dependence, and prolonged transition time.[1–4] It is expected that treatment efficacy and safety profile will be compromised with this kind of formulation. Recently, another delayed-release formulation of 5-ASA, Pentasa® tablets (PT), became available in Taiwan. The clinical efficacy and safety of this preparation in IBD patients has already been demonstrated in various studies.[5–8] PT employs ethylcellulose-coated microgranules which release 5-ASA in the intestinal lumen. After the tablet enters the stomach, it breaks up rapidly into individual microgranules under the action of gastric juice. Released microgranules start to release 5-ASA at this point, independent of pH values. However, the rate of 5-ASA release increases as the pH of the gastrointestinal (GI) tract

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rises.[9] The encapsulation technology used in PT appears to have overcome the disadvantages of the Eudragit resin and has been suggested to provide better therapeutic efficacy than AT.[2] Nevertheless, no direct evidence has been established to validate this conjecture.

A significant portion of IBD patients cannot be maintained in complete remission by AT therapy. This is probably due, at least in part, to the inherent disadvantages of AT, although no direct evidence is available for this claim. Nevertheless, some patients in our clinic have complained about release of 'intact tablets' during defecation. This situation might arise due to pH alterations in the GI tract that affect the release of 5-ASA and the efficacy of AT.[10] This study assessed the efficacy of switching IBD patients with unsatisfactory response from routine AT 2.4 g/day to PT 4 g/day. Efficacy was evaluated by use of the UC disease activity index (UC-DAI) score in UC patients and the CD activity index (CDAI) in CD patients.

Methods

Patients

The study subjects were recruited from patients who had attended our gastroenterology clinic for the management of IBD. These patients had all been managed by routine AT therapy for at least 3 months before switching treatment. Recruited UC subjects were defined endoscopically as prone-to-relapse patients when their endoscopy scores (1 of 4 parameters making up the UC-DAI) were ≥ 2. CD patients were those who underwent AT acute treatment but did not attain a complete remission. A total of 9 UC and 6 CD patients were entered into the study. Inclusion and exclusion criteria are listed in Table 1. The protocol was approved by the Drug Evaluation/Ethics Committee of National Taiwan University Hospital.

Study design

This was an open-label study evaluating UC-DAI[11] (in UC patients) and CDAI[12] (in CD patients) after switching to PT (4 g/day; Ferring A/S, Denmark) therapy from routine AT (2.4 g/day; Tillotts, Switzerland) treatment. PT therapy was administered in a 12-week regimen. Before and after this treatment, patients' UC-DAI or CDAI was determined using published methods (see below).

All subjects were instructed to terminate their AT treatment. PT (500 mg/tablet) were supplied to each study subject on every scheduled visit. They were instructed to take the medication at a dose of 4 g per day (2 tablets, 4 times daily) continuously for 12 weeks.

UC patients

The usual UC-DAI score used successfully in previous trials consists of 4 categories of clinical symptoms — stool frequency, rectal bleeding, endoscopic evaluation, and physician's global assessment. The scoring system was developed by Schroeder et al in 1987.[11] Each category contributes a maximum of 3 points to the final score, which equals the sum of the

Table 1. Inclusion and exclusion criteria of the study.

Inclusion criteria
1) Established diagnosis of ulcerative colitis by sigmoidoscopy, colonoscopy. Diagnosis should be verified by histology.
2) Patient should be maintained with Asacol tablets (2.4 g/day) within the last 3 months.
3) Endoscopic score [Ulcerative Colitis (UC) Disease Activity Index, domain 3] ≥ 2 (only applicable to UC patients).
4) Age > 18 years.
5) Written informed consent obtained.

Exclusion criteria
1) Positive stool culture for enteric pathogens, including *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* species.*
2) *Clostridium difficile*-associated disease.*
3) Positive stool samples for ova or parasites by microscopy.*
4) Pregnant or lactating women.
5) Women of child-bearing potential not taking adequate contraceptive precautions (oral contraceptives or intrauterine device).
6) Chronic use of any anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs (rectally or orally) within 7 days prior to inclusion.
7) Administration of steroids (rectally or orally) within 7 days before entering the study.
8) Administration of any immunosuppressive agents within 90 days before entering the study.
9) Any other disease or condition that may interfere with study assessments as judged by the investigator.
10) Active alcohol or drug abuse.
11) Patients taking part in any other clinical trial.
12) Patients allergic to aspirin or other salicylates.
13) Patients with clinically significant renal/hepatic impairment.
14) Patients presenting any malignant disease.
15) Patients likely not to comply with the study procedures.
16) Patients with any kind of stomy.

*Search for enteric pathogens, ova and parasites should only be performed if relevant, as judged by the investigator.

4 individual scores. Therefore, a patient with very severe disease could have a maximal UC-DAI score of 12.

CD patients

The CDAI score system was initially proposed by Best et al in 1979[12] and has been widely used in various CD clinical trials. The CDAI incorporates 8 Crohn's disease variables that contribute non-proportionally to the final index. CD patients' individual scores for every domain variable were collected from their case report forms. Calculation of the final score was based on the following formula:

$$CDAI = 2(X1) + 5(X2) + 7(X3) + 20(X4) + 30(X5) + 10(X6) + 6(X7) + (X8)$$

where X1 = soft stool frequency; X2 = abdominal pain; X3 = general well-being; X4 = CD symptoms; X5 = frequency of taking diarrhea drug; X6 = presence of abdominal mass; X7 = hematocrit; X8 = body weight. It should be noted that a higher CDAI score represents poorer clinical status.

Both indexes require the patients' self-recording of disease conditions (such as stool frequency and rectal bleeding) in the form of a patient diary, along with investigators' diagnosis and observations. The safety profile during the treatment course was also evaluated. Patients were asked to report any adverse event during each of the scheduled office visits. In addition, blood samples were obtained to determine whether the basic hematological profile and liver and renal functions were altered after the 12-week treatment. At the end of treatment, patients completed a questionnaire used for evaluating the acceptability of the new medication. Fig. 1 shows the design of the study.

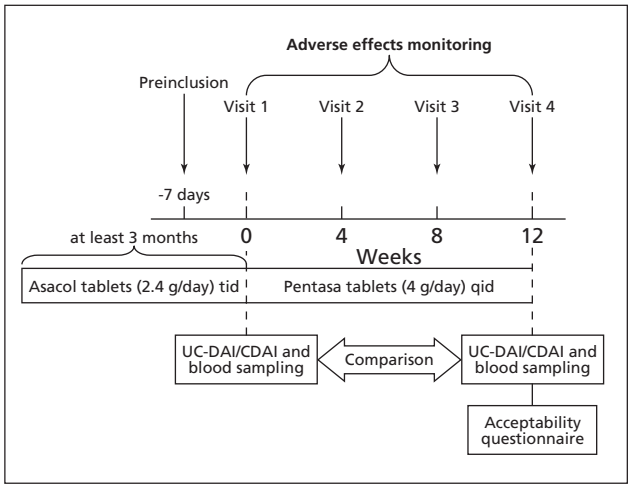

Fig. 1. Schematic representation of the design and schedule of the study. tid = 3 times daily; qid = 4 times daily; UC-DAI/CDAI = ulcerative colitis disease activity index/Crohn's disease activity index.

Statistical analysis

The study design collected pre- and post-PT switch data from the same group of UC or CD patients. The primary analysis was designed to test the null hypothesis that post-PT UC-DAI or CDAI scores were not different from those of pre-PT scores using the Wilcoxon signed rank test. Statistical significance was defined by a p value less than 0.05. Secondary outcomes, such as blood test results, were also compared between pre- and post-PT periods using paired statistics. Patient acceptability results were summarized descriptively.

Results

Patient characteristics

There were 9 men and 6 women recruited into the study. The mean ages of the male and female subjects were 49.9 and 43.8 years, respectively. Mean height and weight were 1.7 m and 69.8 kg, respectively, in males; and 1.5 m and 53.2 kg, respectively, in females.

UC patients

It can be seen in Fig. 2 that UC patients exhibited a mean (± SEM) UC-DAI score of 8.18 ± 0.58 when treated with routine AT. After 12 weeks of PT therapy, the UC-DAI score dropped significantly, to 6.81 ± 0.72 (p = 0.013). In subcategory analysis, it was evident that scores from categories 3 (endoscopy score) and 4 (physician's global assessment) improved significantly, and the reduction of total UC-DAI score was attributed to improvements in these 2 categories. The endoscopy score for these prone-to-relapse UC patients' decreased from 2.22 ± 0.15 to 1.55 ± 0.24.

Patient functional assessment (PFA), that grades patients' subjective feeling of well-being, was also studied as a secondary endpoint. A higher PFA score indicates a diminished feeling of well-being. Although the difference before and after PT treatment was not statistically significant, a modest trend towards improvement was observed (before, 1.41 ± 0.34; after, 1.33 ± 0.39; p = 0.728). Finally, the investigators were asked to subjectively evaluate patients' progress after PT treatment. After PT therapy, 55.5% of the subjects were considered to have improved.

CD patients

The 6 CD patients had a mean (± SEM) baseline CDAI score of 173.10 ± 57.42 at the cessation of AT 2.4 g/day (Fig. 3). After treatment with PT 4 g/day for 12 weeks, their mean CDAI score decreased to 150.45 ± 53.04. Although the difference in CDAI after PT treatment was not significant, there was a trend

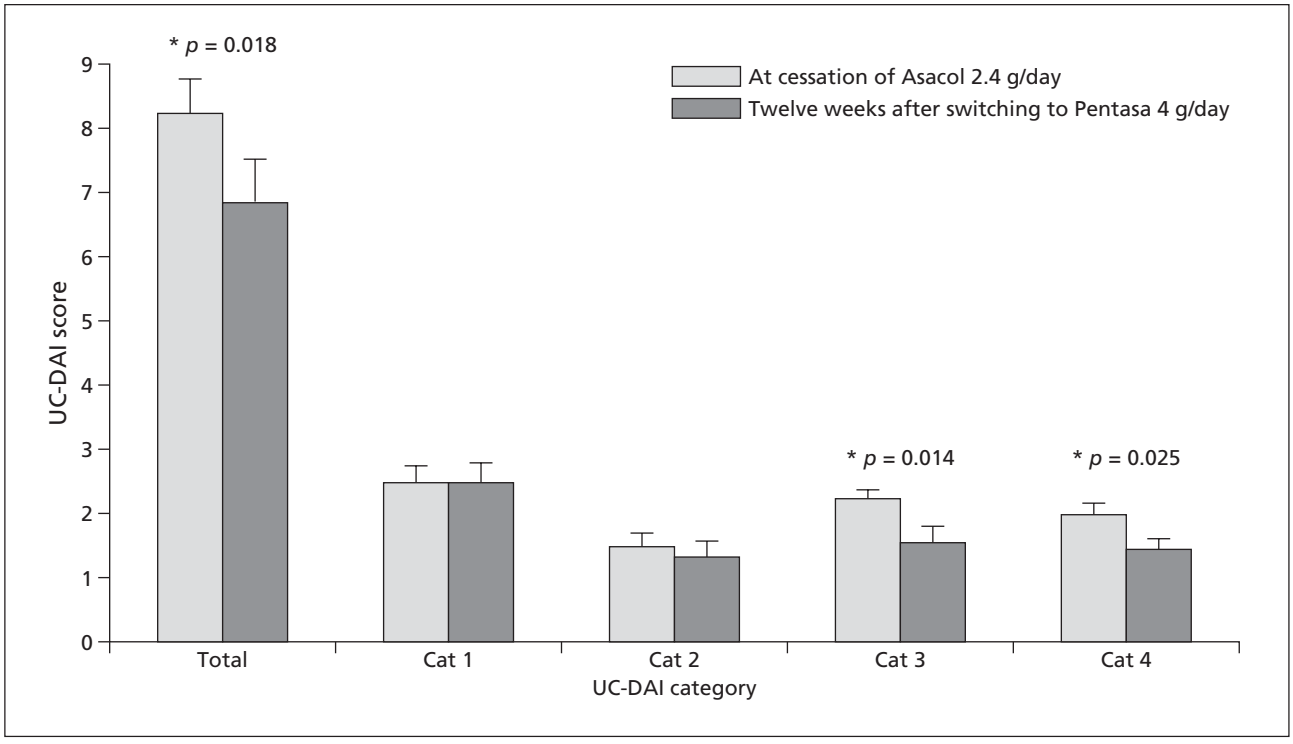

Fig. 2. Ulcerative colitis disease activity index (UC-DAI) scores of 9 prone-to-relapse UC patients before and after switching from Asacol to Pentasa tablet treatment for 12 weeks. Bars represent mean ± SEM of the total scores or score in each individual category. Cat 1 = stool frequency; Cat 2 = rectal bleeding; Cat 3 = endoscopy score; Cat 4 = physician's global assessment.

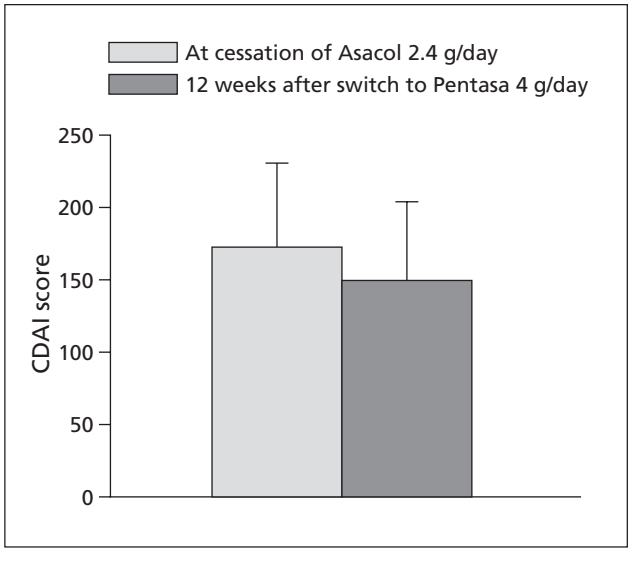

Fig. 3. Crohn's Disease Activity Index (CDAI) of 6 CD patients before and after switching from Asacol to Pentasa tablet treatment for 12 weeks. Bars represent mean ± SEM of the final scores.

towards modestly better therapeutic efficacy with PT 4 g/day.

Safety profile

During the 12-week study period, no adverse event was reported from any of the 15 patients. Blood samples collected before and after the PT course revealed no specific changes in hematological profile or in liver or renal function in either male or female subjects (Table 2).

Patient acceptability

Each subject who completed a course of PT was asked to answer a questionnaire designed to elicit their post-treatment opinions of PT treatment (Fig. 4). The questionnaire was done without interference by the investigators. None of the patients reported difficulties in handling the PT packages; 69.2% reported the absence of uncomfortable feelings during their treatment course; 7.7% reported that intact tablets were found in their stool; and 60.0% preferred PT 4 g/day to their routine AT 2.4 g/day treatment.

Discussion

AT is a well-established maintenance therapy for IBD patients. In our clinic, the majority of UC patients maintained on AT do not attain long-term remission. These patients are usually identified during follow-up endoscopy where the endoscopy index exceeds the criteria for disease remission. These observations are similar to published data in which about 30% of UC patients failed to maintain remission through the use

Table 2. Hematological data (mean ± SEM) of IBD patients at cessation of Asacol 2.4 g/day and 12 weeks after changing to Pentasa 4 g/day.

Variable	At cessation of Asacol 2.4 g/day	After Pentasa 4 g/day for 12 weeks	*p* value	Normal value
Males				
RBC count (10^6/μL)	4.45 ± 0.22	4.55 ± 0.26	0.636	5.2 ± 1.0
Hemoglobin (g/dL)	11.88 ± 0.85	12.02 ± 0.86	0.853	15.3 ± 3.0
Hematocrit (%)	37.50 ± 2.07	38.02 ± 2.55	0.778	40–54
Platelet count (10^3/μL)	310.17 ± 23.01	315.17 ± 30.54	0.887	220 ± 10
Total WBC count (10^3/μL)	7.05 ± 1.05	6.22 ± 0.48	0.372	7.5 ± 3.5
Creatinine (mg/dL)	1.02 ± 0.10	1.13 ± 0.12	0.058	0.8–1.2
Alkaline phosphatase (IU/L)	202.17 ± 16.51	187.17 ± 20.11	0.169	64–238
Females				
RBC count (10^6/μL)	4.23 ± 0.06	3.81 ± 0.09	0.069	4.6 ± 0.9
Hemoglobin (g/dL)	11.80 ± 1.04	11.00 ± 1.28	0.213	13.3 ± 2
Hematocrit (%)	37.28 ± 2.28	34.84 ± 2.50	0.232	37–47
Platelet count (10^3/μL)	327.00 ± 44.35	318.60 ± 51.69	0.786	220 ± 10
Total WBC count (10^3/μL)	10.00 ± 1.44	8.93 ± 1.18	0.216	7.5 ± 3.5
Creatinine (mg/dL)	0.80 ± 0.00	0.80 ± 0.04	1.000	0.6–0.9
Alkaline phosphatase (IU/L)	145.00 ± 25.15	169.60 ± 43.89	0.449	64–238

RBC = red blood cells; WBC = white blood cells.

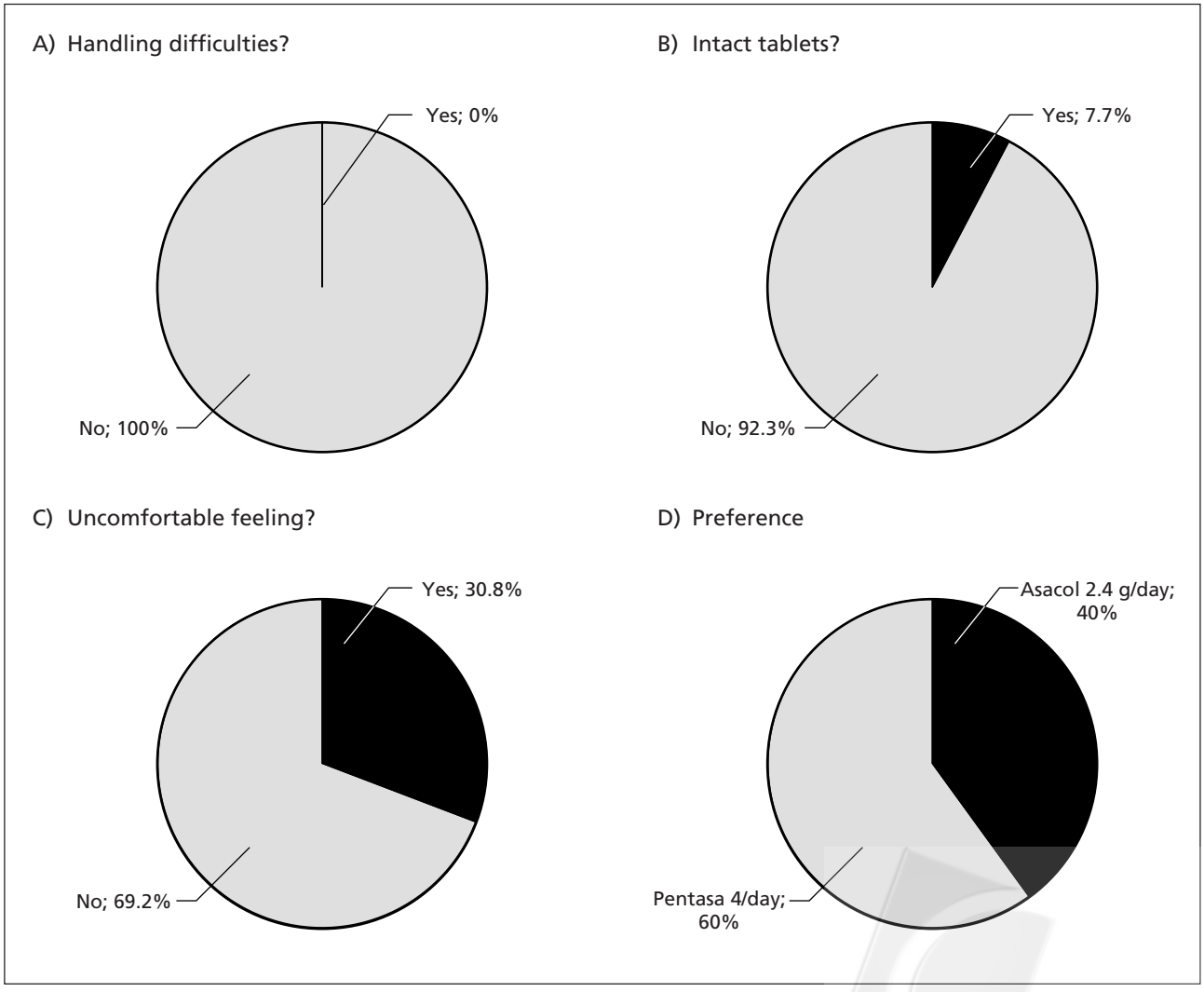

Fig. 4. Patient acceptability responses for Pentasa tablets. A = presence of difficulties in handling the medication; B = presence of 'intact' tablets in stool; C = uncomfortable feeling after use; D = patient's preference as compared to AT.

of AT.[13] In this situation, management of the disease becomes a difficult problem for physicians. Increasing the dose of AT is contraindicated because these patients are often being treated with the maximum dose of the drug (2.4 g/day). The addition of a steroid to the treatment regimen is a typical remedy but, because of side effects, is only a short-term solution. Consequently, there is a need for better forms of therapy for UC patients. The 5-ASA delayed-release mechanism in AT is based on a simple form of encapsulation technology, employing Eudragit acrylic resin.[14] The intrinsic characteristics of Eudragit resin are thought to lead to the clinical disadvantages of AT, such as dose dumping, pH dependence, and prolonged transition time.[1–4] However, there is no direct evidence linking these disadvantages to failure to attain long-term remission.

Although this small-scale study included only 15 IBD patients, PT 4 g/day appeared to have greater efficacy than AT 2.4 g/day, especially in UC patients. The overall UC-DAI score was decreased 16.7% after the 12-week PT 4 g/day regimen as compared to routine AT treatment. Most importantly, the new therapy significantly reduced the endoscopy score of IBD patients. The definition of disease remission in our clinic depends principally on an endoscopy score < 2. Since our results show a reduction in endoscopy score to a mean value of 1.55, these prone-to-relapse patients were rescued to remission after a course of PT. These findings suggest that further improvement might occur in these patients if PT 4 g/day were provided continuously as their maintenance therapy, though a long-term direct comparative study between the two 5-ASA formulations at their maximum doses would be needed to support this claim. The results for CD patients were not conclusive in this study, although there was a tendency for better efficacy and improvement after switching to PT 4 g/day. Further study with increased sample size might lead to statistically significant results.

Unlike AT, PT's delayed-release mechanism is pH-independent. The luminal pH in the lower GI tract of IBD patients has been demonstrated to be lower than normal physiological values.[10,15] These findings might explain the therapeutic weakness of AT, since 5-ASA release might be impaired at lower pH. In addition, the pH-dependence could account for complaints that 'intact' tablets were found during defecation by UC patients taking AT. It is important to note that this phenomenon was only reported by 7.7% of the subjects in this study. The overall safety profiles of PT 4 g/day and AT 2.4 g/day were comparable. A higher preference (60%) for PT 4 g/day may result from the findings that the PT package created no difficulty in handling and that a majority of patients did not experience uncomfortable feelings during treatment.

In the present study, PT 4 g/day was more effective after switching from AT 2.4 g/day in IBD patients, especially those with UC. Despite the difficulty in recruiting IBD patients, a larger scale, direct comparison study between the medications at their maximum dose is needed. With a similar drug safety profile and a higher patient preference, PT 4 g/day could provide an alternative treatment regimen to AT 2.4 g/day for IBD patients.

DECLARATION: The authors certify that they had no affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the manuscript.

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