

Once daily versus conventional dosing of pH-dependent mesalamine long-term to maintain quiescent ulcerative colitis: Preliminary results from a randomized trial

Sunanda Kane¹
William Holderman²
Peter Jacques²
Todd Miodek³

¹Mayo Clinic College of Medicine, Rochester, MN, USA; ²Digestive Health Specialists, Tacoma, WA, USA; ³University of Chicago, Chicago, IL, USA

Background and Aims: Multiple studies have demonstrated the efficacy of aminosaliclates in maintaining remission in ulcerative colitis (UC). A newer formulation of mesalamine can be administered once daily. We aimed to examine the efficacy and tolerability of pH-dependent mesalamine for long-term maintenance, and compare the rates of medication consumption between groups over a prolonged period.

Methods: Subjects whose UC had been quiescent for at least 4 months, and who had been receiving mesalamine for maintenance only, were randomized to once daily or conventional dosing for 12 months. Disease activity and medication consumption was assessed every 3 months. The primary endpoint was the percentage of those with quiescent disease at 12 months.

Results: We enrolled 20 patients, 12 to once daily and 8 to conventional dosing. Six of the 12 patients (50%) in the once daily group compared with 5 of the 8 patients (62.5%) in the conventional group experienced a flare ($p = 0.31$). Only 5 of the 12 (42%) patients in the once daily group were adherent compared with 3 of 8 patients (37.5%) in the conventional dosing group ($p = \text{NS}$). Median amount consumed in the once daily group was 63% (range 0%–100%) and in the conventional group 55% (range 0%–100%), ($p > 0.5$). None of the adherent subjects in the once daily group experienced a flare, while 6 out of 7 (86%) who were non-adherent experienced a flare ($p < 0.01$). In the conventional dosing group, 1 in 3 adherent patients (33%) experienced a flare compared with 4 out of 5 (80%) in the non-adherent group ($p < 0.01$).

Conclusion: Adherence, rather than medication regimen, appeared to be important in disease outcome at 12 months.

Keywords: ulcerative colitis, mesalamine, aminosaliclates, remission

Background

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease of the large intestine characterized by episodes of relapse and remission. Relapses are often not predictable, although factors such as smoking cessation (Silvershtein et al 1994; Fraga et al 1997), chronic non-steroidal anti-inflammatory use (Evans et al 1997; Felder et al 2000) and psychological stress (Levenstein et al 2000) are thought to cause symptom exacerbation in some individuals.

Multiple studies have demonstrated the efficacy of aminosaliclates in maintaining remission in UC (Mesalamine Study Group 1996; Ardizzone et al 1995; Fockers et al 1995; Green et al 1998; Miner et al 1995; Kamm et al 2008). Because of the chronic nature of this disease, therapy must often continue indefinitely. Many patients openly admit that they do not take their medications as prescribed; medication-taking makes patients more uncomfortably aware of their chronic illness status, they have a fear of long-term side effects from medications, and they question the need for medication to treat quiescent disease (Ediger et al 2007).

Correspondence: Sunanda Kane
Associate Professor of Medicine, Miles and Shirley Fiterman Division of Gastroenterology, Mayo Clinic, 200 First Street SW, Rochester MN 55905, USA
Tel +1 507 284 0959
Fax +1 507 266 0335
Email kane.sunanda@mayo.edu

Previous work done at the University of Chicago demonstrated that using objective pharmacy data, rather than patient-derived information, the prevalence of medication non-adherence was 60% in patients with quiescent UC (Kane et al 2001). The average amount of medication consumed was 70% of that prescribed. In a prospective study, those patients who were non-adherent with medications had a higher risk of relapse than those who consumed greater than 80% of their prescribed regimen (Kane et al 2003).

It is difficult to get patients to take medication when they feel well, because the rationale for continued use remains unclear to them. The long-term goals of improving adherence are to reduce frequency of relapse, lower the incidence of long-term complications (ie, colon cancer), and lower overall health costs. Simplifying the medication regimen is one means to increase adherence.

Recently the FDA approved a new formulation of mesalamine to be administered once daily (Kamm et al 2007; Lichtenstein et al 2007). Very good adherence rates were demonstrated, but these rates were gained during controlled trials, rather than in the real world.

A previous short-term pilot trial by this author demonstrated safety and efficacy of pH-dependent mesalamine (Asacol®, Procter and Gamble Pharmaceuticals, Cincinnati Ohio) given once daily, compared with conventional dosing (Kane et al 2003). The aim of this study was to test this hypothesis in a larger number of patients for a longer period of time. We also wished to compare the rates of medication consumption between groups over a prolonged period of time.

Methods

Patients

Adult patients over the age of 18 treated at one of two practices were eligible. Patients must have had documentation of ulcerative colitis by standard criteria, and be in remission for at least 4 months before study entry. Remission for this study was defined clinically, as the absence of all of: blood in the stools, urgency, or cramping. Patients must have been prescribed a regimen of pH-dependent mesalamine (Asacol®), to maintain quiescent disease. Exclusion criteria included documented disease activity in the past 4 months, hospitalization or steroid use for disease activity in the previous 4 months, the use of other preparations of 5-aminosalicylates to treat UC, or the use of other immunomodulators to induce remission. Patients with a history of other diarrheal illnesses such as diarrhea-predominant Irritable Bowel Syndrome, or *Clostridium difficile* colitis, or who were using known diarrheal drugs were

excluded. Before enrollment, the pharmacy of the potential subject was contacted and queried about refill information to establish adherence to previously prescribed mesalamine. Those found to be taking less than 80% of prescribed doses were also excluded.

Protocol

The informed consent of eligible patients was obtained (signed agreement) before participation. As part of the consent process, the updated phone number of the patient's pharmacy was noted. Patients were then randomized to one of two groups: once daily or conventional (twice daily or three times daily) therapy. Randomization was via the use of opaque sealed envelopes, which contained the assignment based on a computer-generated randomization table. Subjects were instructed to conceal their regimen from all research investigators.

Patients were followed prospectively and assessed at 3-month intervals from enrollment. The 3-month and 9-month checks were via telephone contact by one of the study personnel. Disease assessment using the modified Ulcerative Colitis Disease Activity Index (UCDAI) index was performed by personnel in a standard fashion (Appendix A). At time intervals of 6 and 12 months, patients were assessed during a scheduled clinic visit, using the same assessment tool along with a physical exam. Remission was defined as a score of 3 or less. Disease activity, or a flare of disease, was defined as a score >3 or an increase of more than 3 points during the preceding time interval. No additional taking of blood or endoscopy were included in the protocol; lab work and endoscopy were performed for patient care as determined by each treating physician.

Medication consumption rates at months 3, 6, 9, and 12 were calculated using pharmacy data obtained by telephone by study personnel, and the validated formula as described by Steiner and colleagues (Steiner et al 1988). Using the telephone number supplied by the patient, the pharmacy was called to obtain refill information for the previous 3 months. Pharmacists were told that the information was part of an approved research study, investigating the effectiveness of a new regimen of Asacol®. For those patients who used a warehouse service, the date of the patient's request for another supply was recorded and used for the calculation.

The end point of the study was disease relapse or the 12-month study period. An investigator blinded to the subject treatment regimen assessed the outcomes and medication consumption rates for each group. Patients experiencing a flare during the study period were treated as deemed necessary by their treating physician.

Statistics

T-testing was used to compare the means between continuous variables. Chi-square or Fisher's exact test were used to compare frequencies of events between the two groups. Survival analysis was performed to compare relapse rates between the two groups. A *p* value of less than 0.5 was used to signify statistical significance.

A sample size calculation was performed based on the results of the previously published pilot study. Assuming a 15% true difference between the two groups and 90% power, 53 patients would be needed for each group. Because this calculation did not take into account any dropouts, the potential recruitment goal was 70 per treatment arm.

Approval from institutional and local institutional review boards (IRB) was obtained before any patients were enrolled in the study.

Results

Twenty patients were randomized between July 2006 and May 2007. Recruitment was discontinued at this time as a result of the decision by the sponsoring company to proceed with a larger, multi-center study of once daily long-term maintenance therapy. The characteristics of the subjects are listed in Table 1. The groups were well matched and there were no statistical differences in characteristics. The median length of diagnosis was 6 years in both groups; the majority of subjects had pancolitis, and were prescribed 2.4 g of mesalamine for maintenance at the time of enrollment. There was one death during the study, of a patient randomized to the once daily group; the cause of death was cardiac in nature and not felt to be related to medication use or UC directly.

Twelve subjects were randomized to once daily mesalamine for 12 months and 8 to the conventional dosing group. All the patients in the conventional dosing group had

previously been taking their medication bid, and continued to do so during the study. Of the patients from the once daily group, 6/12 (50%) experienced a flare of disease activity (average increase in UCDAI score of 4 points over baseline, with a range of 2–7) during the study period compared with 5/8 patients (62.5%) in the conventional group (*p* = 0.31). The median time to flare was 8 months (range 3–11 months).

Only 5/12 (42%) subjects in the once daily group were adherent to their regimen compared with 3/8 (37.5%) in the conventional dosing group (*p* > 0.05). The median amount consumed in the once daily group was 63% (range 0–100%) and in the conventional group it was 55% (range 0–100%); this was not statistically different (*p* > 0.5).

Of those subjects adherent in the once daily group, 0/5 experienced a flare of disease, while 6/7 (86%) who were non-adherent experienced a flare of disease (*p* < 0.001). In the conventional dosing group, 1/3 adherent patients (33%) experienced a flare of disease compared with 4/5 (80%) in the non-adherent group (*p* < 0.01).

No reported adverse events were felt to be associated directly with once daily therapy; medication was well tolerated at both once and twice daily administrations. The one death that occurred during the study was secondary to myocardial infarction in an elderly male patient with a history of coronary artery disease. The patient had remained in remission at the time of death and the investigators did not feel that his regimen of mesalamine in any way contributed to his death.

Discussion

In this small, randomized cohort of patients, we found that long-term adherence was sub-optimal. Adherence ranged from 0 to 100%, with the median in both groups falling well below the accepted 80% needed for adherence. Indeed, disease activity was significantly associated with non-adherence regardless of prescribed regimen. This result reinforces the principle that continued medication consumption, rather than actual drug regimen, is important in preventing disease relapse.

The clinical outcomes of nonadherence can be detrimental to patients. Researchers have previously shown a correlation between poor adherence and increased frequency of relapses. In the prospective study of 98 patients with quiescent ulcerative colitis, non-adherent patients were found to have more than a 5-fold increased risk of disease relapse compared with those who were adherent (Kane et al 2003).

Non-adherence to 5-aminosalicylic acid (5-ASA)-based therapy has also been linked to an increased risk of developing

Table 1 Patient characteristics

Variable	Once Daily (N = 12)	Conventional (N = 8)	p value
Age, median (range)	44 (22–67)	42 (27–58)	NS
Sex (%M)	58%	62.5%	NS
Length of disease, median (range)	6 (2–25)	6 (3–27)	NS
Extent			
Pancolitis	9	6	NS
Left sided	2	2	NS
Proctitis	1	0	NS
Dose at enrollment, avg (range)	2.4 g (1.6–3.2)	2.4 g (1.6–3.2)	NS

colorectal cancer. Moody et al showed a correlation between nonadherence to, or discontinuation from, sulfasalazine therapy and increased risk of colon cancer (Moody et al 1996). Five out of 152 adherent patients and 5 out of 16 nonadherent patients developed colorectal cancer (X^2 test $p < 0.001$). This finding was supported by Eaden et al who showed in a case-controlled study (102 cases of colorectal cancer in UC with matched controls) that colorectal cancer risk was reduced by 81% in patients receiving regular mesalamine (≥ 1.2 g/day) therapy compared with those taking no treatment ($p = 0.006$) (Eaden et al 2000).

The Manitoba Inflammatory Bowel Disease Cohort Study also looked at the nature of adherence in patients with either Crohn's disease or UC (Ediger et al 2007). Patients from this population-based cohort were queried by postal questionnaire on adherence to a range of therapies to treat inflammatory bowel disease. A total of 35% of patients met the study's criteria for low adherence. Males with UC were significantly more likely to have poor adherence than males with Crohn's disease ($p = < 0.01$). In this study, the investigators found that age was a predictive factor for adherence in females; younger females were less adherent than older females. Males of all ages had comparable levels of adherence and the rate of poor adherence in males was broadly similar to that of the older women (which was a novel finding and contrasted with the results of our previous study where younger males were the least adherent).

Other factors contributing to poor adherence in the Manitoba Cohort study were heavy pill burden and frequent dosing, which are similar findings to those of previous studies. The main factors however, were found to be cost (reported by 25% of patients), reinforcement of status as person with a disease condition (13%), unpleasant side effects (13%), and lack of belief in the effectiveness of the medication (12%).

It is unclear whether continued enrollment in this trial would result in significant differences in outcome or adherence rates between treatment regimens. We saw a significant number of disease flares during this study, but it is unclear whether the inclusion criterion of only 4 months of remission prior to enrollment was too short. The larger maintenance registration trials did not require this length of remission, which again suggests that it may be adherence, in the real world versus controlled trials, that drives improved long-term outcomes. The maintenance study of once or twice daily MMX mesalazine did not find any significant differences in adherence rates between dosing regimens (Kamm et al 2008), but adherence was measured with pill count rather than in a more real world setting as in this study. We did not attempt

any pill counts as patients were seen only every 6 months, and thus it would have been impractical to use this as another means to measure adherence.

The observed tolerability and continued efficacy of once daily pH-dependent mesalamine encouraged the manufacturers after enrollment of 20 patients to undertake a larger, national trial of once daily Asacol® for the maintenance treatment of ulcerative colitis. We did not feel that there were any ethical issues that needed to be addressed with early termination of this study, as patients were being treated with an approved medication and the regimen, not the therapy, was under investigation. These patients were offered enrollment into the larger multi-center trial when the protocol was approved by respective local IRBs.

Because of the documented safety of once or twice daily mesalamine from this and other trials, changing a patient's regimen to once or twice daily seems an appropriate strategy to increase adherence. More importantly however, is patient education on the relationship of continued medication consumption and improved outcomes.

In conclusion, in this small cohort of patients, a pH-dependent formulation of mesalamine is associated with continued disease control if consumed on a regular basis, regardless of daily regimen. Ongoing patient education is key to optimizing long-term outcomes; simplifying regimens is not sufficient to guarantee prolonged quiescent disease.

Disclosure

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Appendix A

Ulcerative Colitis Disease Activity Index

1) No. liquid or verysoft stools per day: _____

2) Abdominal pain, sum of 7 daily ratings: _____

(0 = none, 1 = mild, 2 = moderate, 3 = severe)

3) General well-being: _____

(0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)

4) Complications: (score 1 point per item)

Joint pains _____

Skin or mouth ulcers _____

Eye redness or inflammation _____

Anal fissure _____

5) Bleeding per rectum: _____

(0 = none, 1 = slight, 2 = moderate, 3 = severe)

Score: _____