

Balsalazide Is Superior to Mesalamine in the Time to Improvement of Signs and Symptoms of Acute Mild-to-Moderate Ulcerative Colitis

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OBJECTIVE: Balsalazide is a novel azo-bonded 5-aminosalicylic acid treatment for mild-to-moderate ulcerative colitis. The study objective was to compare symptomatic remission rates with balsalazide and mesalamine while controlling for extent of disease and time since diagnosis in patients with active, mild-to-moderate ulcerative colitis.

METHODS: A total of 173 patients with sigmoidoscopically verified ulcerative colitis were randomized to 8 wk of double-blind treatment with balsalazide 6.75 g/day or mesalamine 2.4 g/day. Both treatments provided 2.4 g/day of oral 5-aminosalicylic acid. Patients maintained symptom diaries throughout the treatment period.

RESULTS: Overall, 46% of balsalazide- and 44% of mesalamine-treated patients achieved symptomatic remission. Higher response rates were noted in newly diagnosed patients with ≤ 40 cm of disease (68% vs 61%) than in recently relapsed patients with >40 cm of disease (36% vs 25%). The median time to symptomatic remission was 12 days shorter with balsalazide (25 days) than with mesalamine (37 days). Significantly more balsalazide patients showed sigmoidoscopic ($p = 0.002$), stool frequency ($p = 0.006$), rectal bleeding ($p = 0.006$), and physician's global assessment score ($p = 0.013$) improvement by 14 days than did mesalamine patients. Similar proportions of patients re-

ported adverse events (54% vs 64%), which were most commonly related to the gastrointestinal and central and peripheral nervous systems.

CONCLUSIONS: Balsalazide is an effective and safe treatment for mild-to-moderate ulcerative colitis. Improvement of symptoms occurs considerably earlier with balsalazide than with mesalamine. (Am J Gastroenterol 2002;97:3078–3086. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Balsalazide is a prodrug that links 5-aminosalicylic acid (5-ASA) with the inert carrier 4-amino-benzoyl- β -alanine (4-ABA). After oral administration, colonic bacteria split balsalazide into 5-ASA and 4-ABA, releasing the active 5-ASA into the colon with minimal systemic absorption of balsalazide, 5-ASA, or 4-ABA (1). Balsalazide administration over a 12-month period has been shown to maintain ulcerative colitis disease remission (2, 3) and in 6- and 12-month studies to be at least as effective as mesalamine in maintaining remission of ulcerative colitis (4, 5). In addition, balsalazide was more effective in preventing relapses in the first 3 months of treatment and provided better control of nocturnal symptoms than did mesalamine (4).

In other comparative clinical trials with mesalamine, balsalazide has been shown to be an effective and safe treatment for acute ulcerative colitis. In a 12-wk study of predominantly newly diagnosed patients (64%) with ulcerative colitis, a significantly greater proportion of patients achieved symptomatic and complete remission, and the time to complete relief of symptoms was significantly shorter with balsalazide treatment than with mesalamine (6). In an 8-wk study of predominately relapsing patients, balsalazide was superior, though not statistically so, to mesalamine in improving the signs and symptoms of ulcerative colitis (7). In all studies, balsalazide has been well tolerated by patients.

Both ulcerative colitis disease history and disease extent could have important influences on the response to mesalamine therapy. Although most studies generally control

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for extent of disease, the effect of duration of disease history has not been formally evaluated; however, because one of the key differences between the patient populations treated in the two previous balsalazide *versus* mesalamine comparative acute studies (6, 7) was the duration of disease history, the present study was designed to allow evaluation of this parameter.

The primary objective of the present clinical study was therefore to further compare the symptomatic remission rate and improvement of individual symptoms of patients with active, mild-to-moderate ulcerative colitis treated with balsalazide to that of patients treated with mesalamine. In addition, the design of the present study stratified patients with respect to time since diagnosis and extent of disease to gain a further understanding of the effect of these variables on the clinical response to these two 5-ASA agents.

MATERIALS AND METHODS

Patients

This multicenter, randomized, double-blind, parallel-group study included 173 otherwise healthy, newly diagnosed, or recently relapsed patients, aged 12–80 yr, with active, mild-to-moderate ulcerative colitis who had at least 12 cm of sigmoidoscopically verified disease. Relapse was defined as requiring an increase in dose or a change in drug therapy. Other inclusion criteria included rectal bleeding and a patient functional assessment score of moderate or severe within the 48 h prior to the screening visit, as well as a sigmoidoscopic score of moderate (friable) or severe (spontaneously bleeding) during flexible sigmoidoscopy without preparation. In addition, women of child-bearing age had to have a negative serum pregnancy test, be practicing a reliable method of contraception, and could not be breast feeding during the study. Patients were excluded if they had experienced more than 5 relapses of ulcerative colitis in the 2 yr preceding the screening visit; used oral, rectal, or intravenous steroids within 14 days, immunosuppressants within 90 days, or 5-ASA-containing agents within 3 days prior to the screening visit; a history of hypersensitivity or failure to respond to 5-ASA agents; severe ulcerative colitis; or had an enteric pathogen. The study protocol was approved by a central Institutional Review Board, and all patients gave written informed consent before undergoing any screening or baseline procedures.

Study Procedures and Drug Treatment

During the 4-day screening/baseline phase, a medical history, ulcerative colitis history, a history of tobacco and nicotine product use, and a listing of concomitant medications were obtained. All patients underwent a physical examination, including body weight and physical signs, an assessment of baseline signs and symptoms, physician's global assessment, sigmoidoscopy with biopsy to confirm ≥ 12 cm of disease and no diagnosis of ulcerative proctitis, and routine clinical laboratory testing. Patient diary entries,

including information on daily bowel events, rectal bleeding, patient functional assessment, and tenesmus, were recorded. Patients returned for assessments on days 14, 28, and 56. At each visit, patients were questioned about their tobacco and nicotine product use and concomitant medications, as well as adverse events. A sigmoidoscopy was performed at each visit, and a second biopsy was obtained at the end of the treatment period.

Patients were classified into four strata at randomization according to time since diagnosis and extent of disease, as follows: 1) newly diagnosed with ≤ 40 cm of disease, 2) newly diagnosed with >40 cm of disease, 3) recently relapsed with ≤ 40 cm of disease, and 4) recently relapsed with >40 cm of disease. Patients were then randomized in a 1:1 ratio to up to 8 wk of oral treatment with either balsalazide 6.75 g/day (COLAZAL, Salix Pharmaceuticals, Raleigh, NC) or mesalamine, pH-dependent, delayed-release tablets 2.4 g/day (Asacol, SmithKline Beecham Pharmaceuticals, Welwyn Garden City, UK). Each study drug treatment was administered three times daily as three capsules (balsalazide active drug or placebo) and two tablets (mesalamine active drug or placebo) to maintain blinding. The total daily dose of each treatment provided an equivalent amount of 5-ASA (2.4 g).

Medications that were not allowed during the treatment period were other 5-ASA products, 4-ASA products, steroids, nonsteroidal anti-inflammatory drugs, >1 dose/day of chronic low-dose aspirin, immunosuppressants, antibiotics, laxatives, antidiarrheals, opiates, bile acid binders, and topical rectal therapies.

The primary efficacy parameter was the proportion of patients in symptomatic remission based on diary card information at the end of 8 wk or at early completion of treatment. Symptomatic remission was defined as patient functional assessment ratings of normal or mild and absence of rectal bleeding. Secondary efficacy parameters included the time to symptomatic remission (time to first occurrence of remission sustained for 3 consecutive days) and the proportion of patients in complete remission, which was defined as symptomatic remission plus a sigmoidoscopic evaluation score of normal or mild. Other secondary efficacy variables were the proportion of patients achieving an improvement in the sigmoidoscopic evaluation score and the change from baseline in the physician's global assessment of disease activity at the end of 8 wk or early completion of treatment. Adverse events were recorded and assessed for severity and relationship to study drug treatment, and changes from baseline in laboratory test results were assessed for their relationship to study drug treatment.

Patient diary symptom scores and the sigmoidoscopic evaluation were rated as normal, mild, moderate, or severe. Data for all recorded days in the patient's diary were used in the assessment of symptomatic remission; missing data were not interpolated from existing days. The physician's global assessment was scored as quiescent, mild, moderate, or severe disease activity, and was based on the physician's

Table 1. Summary of Baseline Demographic and Disease Characteristics by Treatment Group for the Intent-to-Treat and Efficacy-Evaluable Populations

Characteristic	Intent-to-Treat		Efficacy Evaluable	
	Balsalazide (n = 84)	Mesalazine (n = 89)	Balsalazide (n = 73)	Mesalazine (n = 77)
Age (y)	41.6 ± 13.5	40.5 ± 11.9	42 ± 13.6	41.2 ± 12.0
Sex				
Male	45 (54%)	50 (56%)	38 (51%)	41 (53%)
Female	39 (46%)	39 (44%)	35 (48%)	36 (47%)
Race				
White	74 (88%)	80 (90%)	64 (88%)	71 (92%)
Black	8 (10%)	5 (6%)	7 (10%)	3 (4%)
Other	2 (2%)	4 (4%)	2 (2%)	3 (4%)
Nicotine				
User	11 (13%)	12 (13%)	9 (12%)	10 (13%)
Nonuser	73 (87%)	77 (87%)	64 (88%)	67 (87%)
Time since onset of current episode (days)	52.5 ± 73.2	41.3 ± 32.6	54.3 ± 77.2	40.1 ± 31.3
Time since original diagnosis (months)	58.0 ± 79.3	62.8 ± 101.5	56.9 ± 83.9	68.4 ± 106.8
Extent of disease				
≤40 cm	45 (54%)	49 (55%)	41 (56%)	42 (55%)
>40 cm	39 (46%)	40 (45%)	32 (44%)	35 (45%)

Data are presented as mean ± SD or n (%).

overall impression of disease activity after evaluating symptoms collected in the patient diary and the sigmoidoscopic score. The investigator questionnaire, which was used to determine whether the patient was in complete remission or a treatment failure, was completed based on information from the patient diary, sigmoidoscopic evaluation, and the physician's global assessment.

Biopsies obtained at sigmoidoscopy were performed at either 10 cm from the anal verge or the area of the colon with the most severe involvement, if different. The biopsy obtained at the last visit was from the same site biopsied during the screening visit, and biopsies were evaluated by a central study pathologist in a blinded fashion. The evaluation of histologic inflammation was based on epithelial integrity, polymorphonuclear leukocyte invasion of epithelium and crypts, and the degree of chronic mucosal inflammation. Biopsies were classified on a scale of 0 to 4: 0 = inactive colitis; 1 = colitis with mild activity (neutrophils infiltrating epithelium with structural evidence of epithelial injury at one or two foci within mucosa); 2 = colitis with moderate activity (neutrophils infiltrating epithelium with structural evidence of epithelial injury in more than one foci but not diffusely involving submitted mucosa); 3 = colitis with severe activity (neutrophils infiltrating epithelium with structural evidence of epithelial injury, diffusely involving submitted mucosa); and 4 = colitis with active inflammation and erosion.

Statistical Methods

Statistical analyses were conducted on the group of patients who were evaluable and met the criteria for study completion (efficacy-evaluable population) and on all randomized patients who received at least one dose of study drug treatment (intent-to-treat population). The efficacy-evaluable population was defined as patients who met the minimum

symptom requirements at baseline; terminated early because of complete remission or treatment failure, or for other reasons but completed either three of four scheduled visits or two scheduled visits plus an unscheduled early termination visit; received at least 70% of study drug; completed diaries for at least 2 of the 4 days prior to each visit; and who did not have clinically significant protocol violations.

Primary and secondary efficacy parameters were analyzed using the Cochran-Mantel-Haenszel test controlling for strata. For patients terminating early from the study, the last observation was carried forward and used as the study endpoint in the analyses. The median time to symptomatic remission was determined from a Kaplan-Meier analysis using a Wilcoxon scoring procedure. Between-group comparisons of treatment-emergent adverse events occurring in ≥5% of patients in either treatment group were performed using Fisher's exact test. Statistical significance was declared at the 0.05 level of significance.

RESULTS

There were no differences between treatment groups in the baseline demographic and disease characteristics of the 173 enrolled patients who received study drug treatment (Table 1). The majority of patients were white, did not use nicotine, and had been diagnosed with ulcerative colitis approximately 5 yr before study entry. There was a slightly higher proportion of patients who were male and had ≤40 cm of disease. The majority of patients in both treatment groups assessed their symptoms as moderate to severe at study entry. The only significant difference between groups at entry was in the distribution of sigmoidoscopic severity scores ($p = 0.04$). This difference was due to a greater percentage of mesalamine-treated than balsalazide-treated

patients entering with a sigmoidoscopic score of severe (28% vs 15%); efficacy analyses were, therefore, controlled for baseline sigmoidoscopic score. However, there was no evidence from any of the other disease symptom scores that patients randomized to mesalamine had more severe disease activity. They did, however, report a duration of the current relapse that was, on average, 11 days shorter than that reported by patients randomized to receive balsalazide (Table 1).

Patients meeting the predefined criteria for complete remission or treatment failure were allowed to discontinue the study prior to 8 wk treatment. Data for these patients was carried forward in the analysis. Equal numbers of patients from each drug-treatment group discontinued early from the study. The principal reasons for discontinuation, other than administrative (*i.e.*, lost to follow-up), were that patients achieved complete remission (18 balsalazide, 17 mesalamine), were considered treatment failures (11 balsalazide, 13 mesalamine), or experienced an adverse event (3 balsalazide, 6 mesalamine).

Efficacy

Symptomatic remission at endpoint, the primary efficacy parameter, was achieved by 52% (38/73) of patients treated with balsalazide and 49% (38/77) of those treated with mesalamine in the efficacy-evaluable population. The results were similar for the intent-to-treat population: 46% (39/84 patients) vs 44% (38/89), balsalazide vs mesalamine, respectively.

Although no statistically significant differences between the two therapies were detected at the end of 8 wk of treatment, differences were detected between the various strata in the rates at which each group achieved symptomatic remission. Patients in stratum 1 were most responsive to treatment (intent-to-treat population: 68% balsalazide, 61% mesalamine), whereas those in stratum 4 were least responsive (intent-to-treat population: 36% balsalazide, 25% mesalamine) (Fig. 1). Significantly more patients treated with balsalazide in stratum 1 achieved symptomatic remission at day 14 than did mesalamine-treated patients (intent-to-treat population: 42% vs 13%, $p = 0.035$) (Fig. 1). By day 56 and endpoint, the percentages of patients achieving symptomatic remission were similar for both treatments in all strata.

Patients treated with balsalazide achieved symptomatic remission earlier than did patients treated with mesalamine, 25 vs 37 days (median time) (Fig. 2). Although the difference between groups in time to symptomatic remission was 12 days, it was not statistically significant in the nonstratified analysis. In stratum 1, the median time to symptomatic remission was significantly less with balsalazide than with mesalamine (11 vs 22 days, $p = 0.031$). In strata 2 and 3, balsalazide-treated patients also had a shorter median time to symptomatic remission compared with mesalamine-treated patients (25 and 37 days for balsalazide vs 33 and 40 days for mesalamine, strata 2 and 3 respectively); there was no difference in stratum 4 (43 vs 42 days).

The overall rates of complete remission were 46% for balsalazide and 41% for mesalamine at endpoint. Similar to the findings for symptomatic remission, patients in stratum 1 were most responsive (68% balsalazide, 57% mesalamine), and those in stratum 4 were least responsive (36% and 25%). Within the strata, patients treated with balsalazide tended to achieve complete remission earlier than did patients treated with mesalamine. In stratum 1, 16% of balsalazide versus 4% of mesalamine-treated patients were in complete remission by day 14. Supporting the findings for complete remission are the biopsy results showing a higher proportion of balsalazide-treated patients with inactive colitis at endpoint (Table 2). The proportions of patients with biopsy findings indicating inactive colitis increased from 5% at baseline to 49% at endpoint in the balsalazide group and from 4% to 39% in the mesalamine group.

Other secondary efficacy parameters also favored balsalazide over mesalamine (Fig. 3), and the patterns of improvement were similar to those reported above for symptomatic and complete remission (generally greatest improvement in stratum 1 and earlier improvement with balsalazide). At day 14, a significantly greater proportion of patients treated with balsalazide than with mesalamine demonstrated improvement in all secondary efficacy parameters. Significantly more balsalazide patients showed sigmoidoscopic ($p = 0.002$), stool frequency ($p = 0.006$), rectal bleeding ($p = 0.008$) and physician's global assessment score ($p = 0.013$) improvement by 14 days than did mesalamine patients. The difference was still significant at day 28 for improved sigmoidoscopic score (Fig. 3). By the day 56 and endpoint evaluations, there were no significant differences between treatment groups in the nonstratified analysis.

An additional secondary analysis was undertaken to examine the independent influence of extent of disease and time since diagnosis on the therapeutic response. For this analysis, the hallmark symptom of rectal bleeding was used because all patients entered the study with rectal bleeding. There were no between-group differences at entry in the severity of rectal bleeding ($p = 0.456$); however, when the proportion of patients whose rectal bleeding had resolved was compared, there were clear differences favoring balsalazide for patients with left-sided disease (without regard to disease history) and for newly diagnosed patients (without regard to disease extent). This outcome is shown in Figure 4 as an odds ratio comparison at both the day 14 and day 56 evaluations. Both of these patient subgroups responded more robustly to balsalazide at the day 14 evaluation and by day 56, the greater response of the left-sided disease patients to balsalazide over mesalamine was still maintained.

Safety

A similar number of patients in each treatment group withdrew from the study because of an adverse event (three balsalazide, five mesalamine). In addition, one patient in the balsalazide group discontinued owing to *Clostridium diffi-*

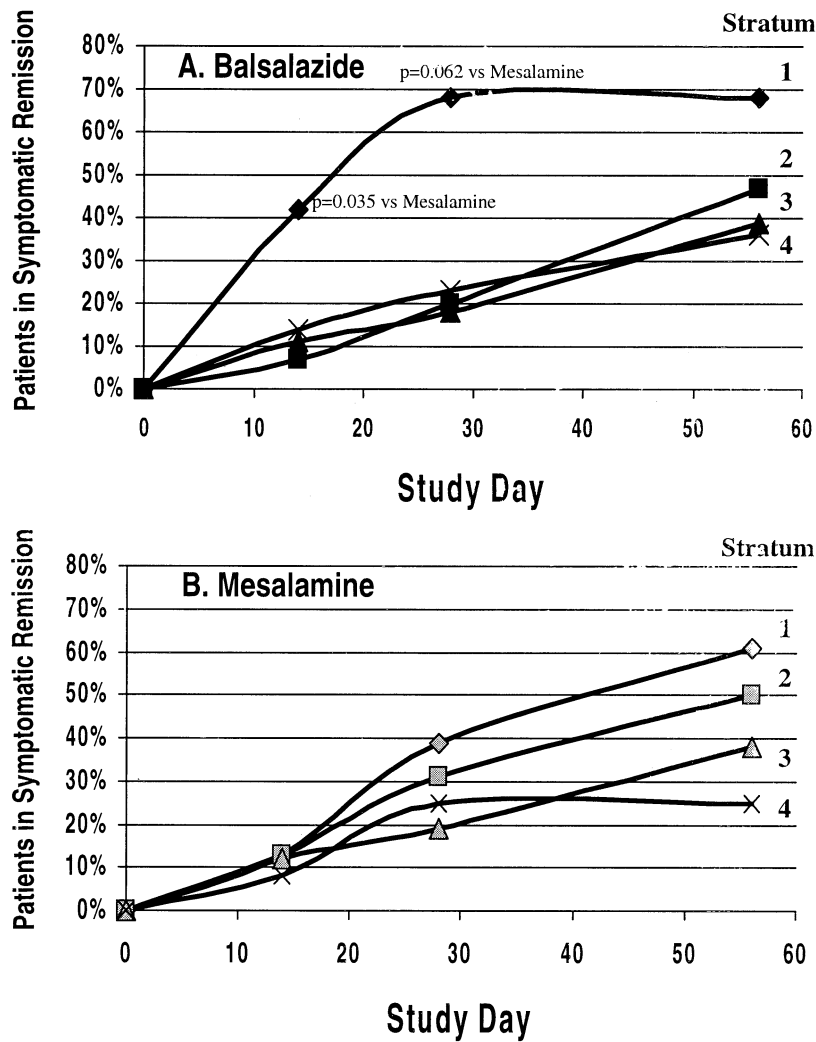


Figure 1. Analysis of symptomatic remission in the intent-to-treat patients by stratum. The percentage of patients achieving symptomatic remission at each clinic visit are shown. Stratum 1 = newly diagnosed, ≤ 40 cm of disease; stratum 2 = newly diagnosed >40 cm of disease; stratum 3 = recently relapsed, ≤ 40 cm of disease; stratum 4 = recently relapsed, >40 cm of disease. *P* values represent the comparison of the stratum 1 balsalazide-treated patients with the stratum 1 mesalamine-treated patients. Statistical comparison used the Cochran-Mantel-Haenszel test controlling for entry sigmoidoscopic score.

cile infection. During the 8-wk treatment period, 54% of balsalazide- and 64% of mesalamine-treated patients reported at least one treatment-emergent adverse event (Table 3). The most commonly reported adverse events ($\geq 5\%$ incidence in either treatment group) were headache (11% vs 16%), nausea (10% vs 15%), diarrhea (7% vs 9%), vomiting (7% vs 1%), abdominal pain (6% vs 13%), insomnia (5% vs 3%), cough (5% vs 1%), and flatulence (5% vs 6%). None of the differences were statistically significant. Although the greatest number of adverse events were related to the gastrointestinal system (32% vs 36%, balsalazide vs mesalamine), the majority were not considered to be treatment related. The exceptions were nausea, which was considered related to balsalazide in 4 of 8 cases, and abdominal pain, which was considered related to mesalamine in approximately 6 of 12 cases. There were no clinically significant changes in any laboratory test results in either treatment

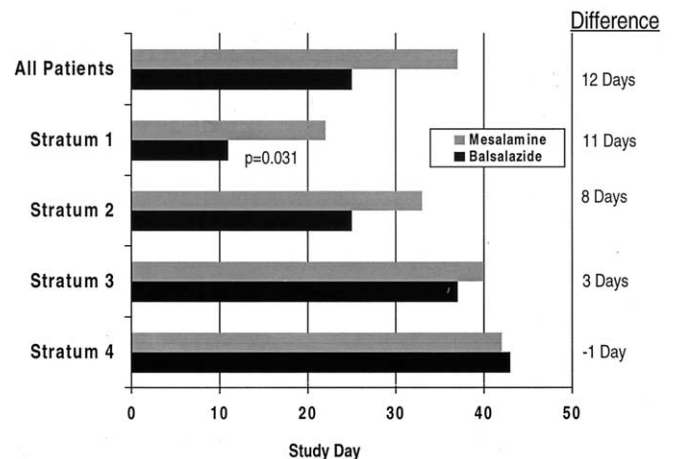


Figure 2. Median time to symptomatic remission in the intent-to-treat population. Values shown are the median times derived from the overall Kaplan-Meier plots for each strata.

Table 2. Summary of Biopsy Severity by Treatment Group for the Intent-to-Treat Population

Time Point	Severity	Balsalazide	Mesalamine
Baseline		n = 80	n = 81
	Inactive	4 (5%)	3 (4%)
	Mild	21 (26%)	19 (23%)
	Moderate	31 (39%)	26 (32%)
	Severe	8 (10%)	11 (14%)
Endpoint		n = 72	n = 72
	Inactive	35 (49%)	28 (39%)
	Mild	12 (17%)	12 (17%)
	Moderate	6 (8%)	10 (14%)
	Severe	8 (11%)	6 (8%)
	Erosion	11 (15%)	16 (22%)

group, and all values remained within normal limits. In addition, there were no treatment-related differences in vital signs; however, a significantly greater proportion of patients treated with balsalazide gained weight and fewer balsalazide-treated patients lost weight than those patients treated with mesalamine ($p = 0.040$).

DISCUSSION

The results of the present study demonstrate that 8 wk of balsalazide treatment is as effective as mesalamine in patients with mild-to-moderate ulcerative colitis. At the endpoint evaluation, approximately 50% of the efficacy-evaluable patients in both treatment groups had achieved

symptomatic remission. Newly diagnosed patients were the most responsive to both treatments (68% vs 61%, stratum 1; 47% vs 53%, stratum 2), whereas recently relapsed patients were least responsive (39% vs 40%, stratum 3; 36% vs 25%, stratum 4); however, balsalazide was superior to mesalamine in the time to symptomatic remission. Overall, patients treated with balsalazide achieved symptomatic remission 12 days earlier than did patients treated with mesalamine. In addition, in stratum 1, significantly more patients treated with balsalazide had achieved symptomatic remission at day 14 (42% vs 13%; $p = 0.035$), and at day 28, there was still a substantially higher proportion of balsalazide-treated patients in symptomatic remission (68% vs 39%).

Although equal numbers of patients in each treatment group withdrew early from the study because of complete remission (18 balsalazide, 17 mesalamine) or treatment failure (11 balsalazide, 13 mesalamine), it is possible that the primary efficacy outcome would have been different had these patients remained on treatment. For example, patients attaining early remission might have deteriorated upon further treatment, whereas early treatment failures may have continued to improve their symptoms. Although the data from these patients was carried forward in the analysis, the overall effect of allowing early termination may have reduced the statistical power of the study; however, at least for patients withdrawing due to treatment failure (worsening in rectal bleeding, stool frequency, or sigmoidoscopic score by

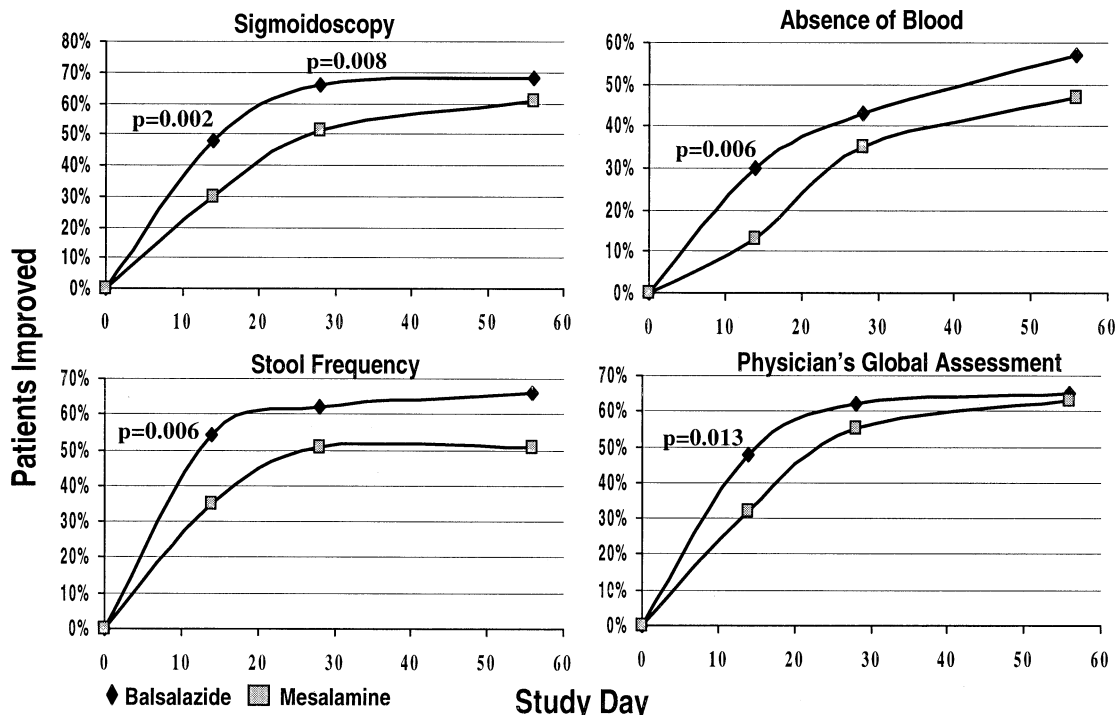


Figure 3. Improvement in signs and symptoms of disease in the intent-to-treat population. The percentage of patients improving by one severity grade or more (sigmoidoscopic score, stool frequency, or physician's global assessment) or achieving an absence of rectal bleeding at each clinic visit are shown. The statistical comparison used the Cochran-Mantel-Haenszel test controlling for entry sigmoidoscopic score.

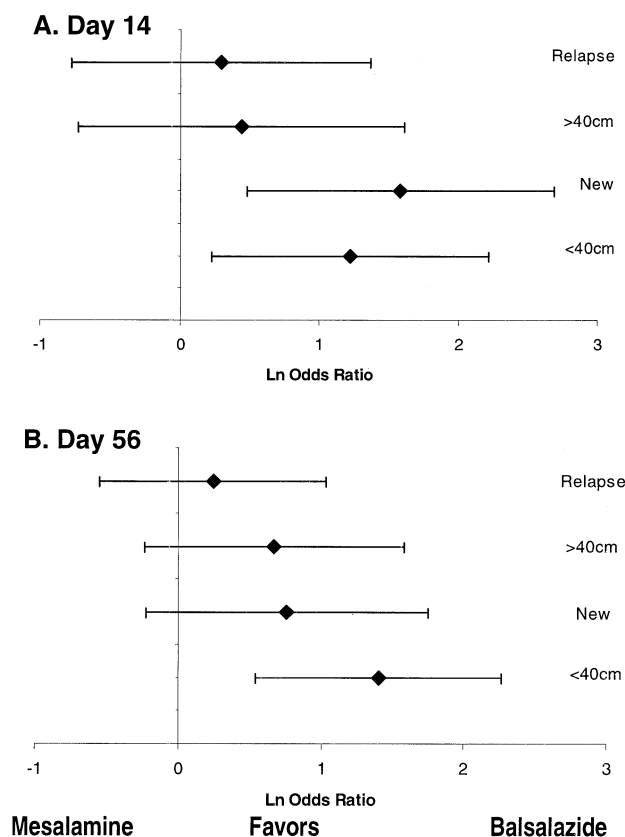


Figure 4. Influence of extent of disease and disease history on the proportion of balsalazide or mesalazine-treated patients achieving an absence of rectal bleeding at evaluation day 14 (A) or day 56 (B) in the intent-to-treat population. The bars show the 95% confidence intervals for the natural log of the odds ratio. Positive values favor balsalazide over mesalazine.

2 wk), this allowance was certainly consistent with standard clinical practices for the treatment of acute ulcerative colitis.

Other efficacy parameters showed a similar pattern of improvement. Although improvement was similar, but generally greater, after 8 wk of treatment in patients treated with balsalazide, improvement occurred significantly earlier, and in a higher proportion of patients, with balsalazide than with mesalazine treatment. At day 14, a significantly higher proportion of patients treated with balsalazide had improvement in the sigmoidoscopic score, stool frequency, rectal bleeding, and physician's global assessment score. The more rapid response to balsalazide treatment in sigmoidoscopic score improvement and in the absence of rectal bleeding may reflect that these endpoints directly measure the extent of inflammation in the left colon.

Patients with left-sided disease showed the greatest and most persistent between-treatment group differences for rectal bleeding cessation as measured at day 14 and day 56 of the study. In addition, newly diagnosed patients, regardless of disease extent, were also more sensitive to the action of balsalazide than mesalazine at the 14-day evaluation point. It is likely that this large difference in response for this hallmark symptom of ulcerative colitis was responsible for

Table 3. Summary of Treatment-Emergent Adverse Events Reported by $\geq 5\%$ of Patients in Either Treatment Group

	Balsalazide (n = 84)	Mesalazine (n = 89)
Patients with AEs		
Serious AEs	0 (0%)	2 (2%)
Withdrawals owing to AEs	3 (4%)	6 (7%)
Number with AEs	45 (54%)	57 (64%)
Number with causally related AEs	20 (24%)	24 (27%)
Common AEs (% of patients)		
Headache	9 (11%)	14 (16%)
Nausea	8 (10%)	13 (15%)
Abdominal pain	5 (6%)	12 (13%)
Fever	3 (4%)	9 (10%)
Diarrhea	6 (7%)	8 (9%)
Vomiting	6 (7%)	1 (1%)
Arthralgia	4 (5%)	6 (7%)
Pharyngitis	3 (4%)	6 (7%)
Fatigue	3 (4%)	6 (7%)
Flatulence	4 (5%)	5 (6%)
Insomnia	4 (5%)	3 (3%)
Rhinitis	4 (5%)	3 (3%)
Cough	4 (5%)	1 (1%)

Patients reporting the same adverse event more than once were counted once per event and once per body system. AE = adverse event.

the superior time to symptomatic remission observed for stratum 1 (newly diagnosed, left-sided) patients.

Treatment of active ulcerative colitis in patients with left-sided or distal disease can be particularly challenging when oral 5-ASA therapies are employed. Several comparative studies (8–10), as well as a recent meta-analysis (11), have documented the enhanced efficacy of topical 5-ASA treatments over oral delayed-release mesalazine treatments for distal UC and for the oral plus topical treatment of left-sided UC (9). The more rapid response to balsalazide treatment, particularly in the left-sided patient, may be related to the reliability of the azo-bonded delivery system to all areas of the colon. In contrast, the delivery system for the mesalazine product used in this study relies on a pH-dependent mechanism to deliver 5-ASA to the colon (12). Alterations in intestinal transit time and pH that may occur in association with acute ulcerative colitis and diet may result in variable dissolution of the mesalazine tablet, which can lead to inconsistent delivery of effective amounts of 5-ASA to the distal colon (13, 14). In a recent pharmacokinetic study (15), this limitation of the pH-dependent mesalazine delivery system was found not to be overcome by providing increased oral doses of mesalazine. In that study, no increase in rectal biopsy tissue levels of 5-ASA or N-acetyl-5-ASA were found when the oral dose was increased from 2.4 g daily to 4.8 g daily, although plasma mesalazine levels increased more than two-fold. In contrast, the diazo bond in balsalazide linking 5-ASA with 4-ABA is dependent on the presence of bacterial azoreductase found only in and throughout the colon (1). Thus, because delivery of efficacious amounts of azo-bonded 5-ASA to the distal colon is not greatly influenced by the disease process or variable pH, use of balsalazide may

translate into greater efficacy earlier in treatment and particularly for patients with more distal disease.

In addition to achieving an early response, balsalazide treatment was well tolerated by patients. Similar proportions of patients in both treatment groups reported adverse events, and few treatment-emergent adverse events were considered treatment-related or serious. Of interest was that a significantly greater proportion of balsalazide-treated patients gained weight and a smaller proportion lost weight compared with patients treated with mesalamine. This difference in weight changes with balsalazide treatment may reflect the earlier improvement of disease symptoms, thereby leading to a slowing of the weight loss commonly associated with active ulcerative colitis (16).

Patients entering into the study were excluded if they had more than five relapses in the prior 2 years, had severe disease, or had failed to respond to an increase in dose of a 5-ASA therapy used to treat their current relapse. The patient population examined in this study might therefore be considered more likely to respond to either 5-ASA treatment than the overall ulcerative colitis patient population. It is therefore of interest that even in this "5-ASA-favored" population, the influence of time since diagnosis produced such a measurable influence on the responsiveness to either of these 5-ASA agents. The concept that disease progression may result in 5-ASA resistance has not been reported even though it may be commonly accepted in clinical practice. Aminosalicylates have a wide range of molecular actions through which they exert their anti-inflammatory effects. Among these are antioxidant activities (17, 18), inhibition of eicosanoid mediator production (19, 20), reduction in antibody production by B-cells (21), and inhibition of expression of genes encoding proinflammatory cytokines through inhibition of nuclear factor κ B activation (22, 23). It is not surprising that a 5-ASA naïve patient may have the full range of these various pathways intact and available for 5-ASA action; however, a patient with more progressive, relapsing disease who has previously been exposed to these agents may have experienced "down-regulation" in certain 5-ASA responsive elements, rendering that patient less responsive through a more select subset of molecular pathways. Further clinical experimentation to delineate mechanisms responsible for patient responsiveness to mesalamine agents is clearly warranted and would benefit the clinical treatment of ulcerative colitis patients.

In conclusion, 8 wk of treatment with balsalazide is as effective and safe as mesalamine in patients with mild-to-moderate ulcerative colitis. Balsalazide treatment, however, results in earlier symptomatic remission of acute ulcerative colitis, which is associated with healing of the disease process (reduction in inflammation and rectal bleeding). Balsalazide may be a more advantageous choice than mesalamine for treating acute ulcerative colitis because it provides rapid symptomatic relief in all patients and more effectively treats patients with left-sided and distal disease than mesalamine.

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