

A COMPARISON OF BUDESONIDE AND MESALAMINE FOR ACTIVE CROHN'S DISEASE

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ABSTRACT

Background Crohn's disease is often treated with glucocorticoids or mesalamine. We compared the efficacy and safety of controlled-ileal-release budesonide capsules and slow-release mesalamine tablets in patients with active Crohn's disease affecting the ileum, the ascending colon, or both.

Methods In a double-blind, multicenter trial, we enrolled 182 patients with scores of 200 to 400 on the Crohn's Disease Activity Index (with higher scores indicating greater disease activity) and randomly assigned 93 to receive 9 mg of budesonide once daily and 89 to receive 2 g of mesalamine twice daily for 16 weeks. The primary efficacy variable was clinical remission, defined as a score of 150 or less on the Crohn's Disease Activity Index.

Results In the analysis of all patients who received at least one dose of study drug, the rates of remission after 8 weeks of treatment were 69 percent in the budesonide group and 45 percent in the mesalamine group ($P=0.001$); the respective rates after 16 weeks of treatment were 62 percent and 36 percent ($P<0.001$). Seventy-seven patients in the budesonide group completed the 16 weeks of treatment, as compared with 50 patients in the mesalamine group ($P<0.001$). The numbers of patients with adverse events were similar in the two groups, but those assigned to budesonide had fewer severe adverse events. Among patients who completed 16 weeks of treatment, the morning plasma cortisol value was normal in 67 percent of budesonide-treated patients and 83 percent of mesalamine-treated patients ($P=0.06$); 90 percent and 100 percent, respectively, had normal increases in cortisol in response to cosyntropin ($P=0.02$).

Conclusions In patients with active Crohn's disease affecting the ileum, the ascending colon, or both, a controlled-ileal-release formulation of budesonide was more effective in inducing remission than a slow-release formulation of mesalamine. (N Engl J Med 1998;339:370-4.)

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CROHN'S disease is a chronic inflammatory disorder of the bowel whose cause is unknown. During the acute phase of the disease, glucocorticoids such as prednisolone and prednisone are commonly used.^{1,2} However, this treatment is often associated with clinically important side effects, such as moon face, hirsutism, and acne.

Budesonide is a glucocorticoid that is a highly potent topical antiinflammatory agent with lower systemic activity than conventional glucocorticoids,³ because it is nearly 90 percent metabolized during its first pass through the liver to forms with minimal or no steroidal activity.³ Budesonide capsules contain granules that allow the slow release of the drug, mainly in the ileum and the ascending colon. Thus, this topical treatment for Crohn's disease has a reduced risk of glucocorticoid-associated side effects.

In a placebo-controlled, dose-finding study, this form of budesonide was significantly more effective than placebo in inducing remission of active Crohn's disease affecting the ileum and the ascending colon, with an optimal daily dose of 9 mg.⁴ This dose of budesonide has also been found, in two studies, to be as effective as oral prednisolone,^{5,6} but with fewer glucocorticoid-associated side effects.

Slow-release formulations of mesalamine that facilitate delivery of the drug to the small intestine are often used as first-line treatment in patients with Crohn's disease that is mild to moderately active, although results of controlled studies are conflicting.⁷⁻¹⁰ We compared the efficacy and safety of budesonide and mesalamine for active Crohn's disease.

METHODS

Selection of Patients

The study was performed between November 1994 and August 1996. Eligible patients were at least 18 years of age and had a confirmed diagnosis of active Crohn's disease, as defined by a score of 200 to 400 on the Crohn's Disease Activity Index. The index assesses eight variables: the number of liquid stools, the extent of abdominal pain, general well-being, the occurrence of extraintestinal symptoms, the need for antidiarrheal drugs, the presence of abdominal masses, hematocrit, and body weight.¹¹ Scores can range

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from 0 (no active disease) to 700 (severe disease). Scores of 151 to 400 are associated with disease that is mild to moderately active. Scores of 150 or less are considered to indicate remission.

To be eligible, patients had to have disease that was confined to the distal ileum, the ileocecal region, and the ascending colon, except for scattered aphthous ulcers, and was verified by colonoscopy, small-bowel follow-through, or barium enema within 24 months before randomization. Patients with active Crohn's disease in the rectum were not eligible, nor were those with septic complications, abscess, perforation or active fistulas, ileostomy, or colostomy; those who had undergone resection of more than 100 cm of the ileum; or those who required immediate surgery. No patient received immunosuppressive drugs within three months before the study or glucocorticoids or more than 2 g of mesalamine per day within two weeks before the study. Patients with diabetes mellitus, active peptic ulcer disease, systemic infection, or clinically significant renal, hepatic, or cardiovascular disease or asthma were ineligible, as were pregnant or breast-feeding women and patients who were allergic to glucocorticoids or mesalamine.

The study was approved by the institutional review board at each center and was conducted according to the principles of the Second Declaration of Helsinki. All participants provided written informed consent.

Study Medication

The budesonide formulation used is a gelatin capsule containing acid-stable microgranules (Entocort, 3-mg capsules, Astra Draco, Lund, Sweden). The microgranules (each measuring approximately 1 mm) are composed of an inner sugar core surrounded by a layer of budesonide in ethylcellulose and an outer acrylic-based resin coating (Eudragit L100-55) that dissolves at a pH of 5.5 or higher. The mesalamine formulation (Pentasa, 500-mg tablets, Ferring, Vanløse, Denmark) disintegrates in the stomach into several hundred microgranules (each measuring approximately 1 mm) that are coated with ethylcellulose, so that mesalamine is released slowly throughout the gastrointestinal tract. Placebo medications were identical in appearance and taste to the investigational drugs.

Design of the Study

The trial was a randomized, double-blind, double-dummy study performed at 25 centers in Denmark, France, the United Kingdom, Norway, Italy, Spain, Portugal, Greece, South Africa, Austria, Australia, and Ireland. Randomization of patients in permuted blocks of four was performed separately at each center with sealed, opaque treatment-code envelopes. Treatment was scheduled to last 16 weeks. Patients received 9 mg of budesonide once daily (and a placebo once daily) or 2 g of mesalamine twice daily. Compliance was assessed by pill counts.

At entry, each patient's demographic characteristics, medical history, current and past diagnoses, and current medications were recorded. Sigmoidoscopy of the distal part of the colon was performed to rule out rectal inflammation. Disease activity was assessed with the Crohn's Disease Activity Index before treatment; after 2, 4, 8, 12, and 16 weeks of treatment; and in the event that treatment was discontinued. Efficacy was not evaluated after the discontinuation of treatment in patients who withdrew from the study before week 16. At each visit, a physical examination, quality-of-life assessment, laboratory tests, and a global evaluation were conducted and patients were asked whether any adverse events had occurred. At week 16, within 24 hours after the last dose of medication, adrenal function was assessed between 8 and 10 a.m. by the administration of cosyntropin. No medication for Crohn's disease other than the study drugs was allowed. Loperamide or opiates to control diarrhea were allowed.

Quality of life was assessed with the self-administered Psychological General Well-Being index,¹² which includes 22 questions covering six categories (anxiety, depressed mood, positive well-being, self-control, general health, and vitality). The worst possible score is 22, and the best possible is 132.

The patients were asked to record on diary cards their intake of study medication, the frequency of loose stools, the extent of abdominal pain, and general well-being during the seven days before each visit. Blood samples were taken for hematologic and biochemical assessments, liver-function tests, and measurements of indicators of inflammatory activity (the erythrocyte sedimentation rate and C-reactive protein levels). Blood was drawn for measurements of plasma cortisol at the time intravenous cosyntropin (Synacthen, Ciba-Geigy, Summit, N.J.) was administered and 30 and 60 minutes later. A normal response was defined as an increase in the plasma cortisol concentration of 7.2 μg per deciliter (200 nmol per liter) from base line or an absolute value above 18.1 μg per deciliter (500 nmol per liter) at 30 or 60 minutes.

All adverse events were recorded, whether or not they were considered to be related to the study medication. A serious adverse event was defined as one that was life threatening or led to permanent disability, hospitalization, or death. The intensity of adverse events was graded as mild, moderate, or severe, with a severe event considered to be one that was incapacitating, leading to an inability to work or take part in normal activities. Patients could be withdrawn from the study at any time if their physicians believed their condition had substantially deteriorated.

Statistical Analysis

We estimated that 85 patients were needed in each group in order to detect a difference of 22 percent between groups in the proportion of patients in remission, assuming a remission rate of 50 percent with budesonide treatment. The primary outcome was the remission rate. The primary analysis (as stated in the study protocol) included all patients who received at least one dose of study medication. Patients who were found to be ineligible after randomization and patients who were less than 85 percent compliant with treatment were excluded from the per-protocol analysis (but were included in the analysis according to the intention to treat). The study protocol called for an investigation of the influence of prognostic factors on remission rates by two-way analysis of variance, with treatment, subgroup (e.g., sex), and the interaction of treatment and subgroup as factors. Secondary end points were a decrease in the Crohn's Disease Activity Index of at least 100 points or a score of 150 or less (or both), other changes in this score, the length of time to remission, changes in the Psychological General Well-Being index, changes in adrenal function, and adverse events.

The chi-square test was used to compare proportions. The time to the discontinuation of treatment and the time to remission were analyzed by Kaplan-Meier estimates and a generalized Wilcoxon test.¹³ Student's *t*-test, Wilcoxon's test, and analysis of variance were used to assess quantitative variables. All tests were two-sided. *P* values of less than 0.05 were considered to indicate statistical significance.

For analysis of remission rates at 2, 4, 8, 12, and 16 weeks, we divided the number of patients in the group who were evaluated and in remission at that time or who had already been withdrawn from the study while in remission by the number of patients who were evaluated at that time or who had withdrawn before that time and who had been evaluated at least once during treatment. The secondary end point of a decrease in the Crohn's Disease Activity Index of at least 100 points or a score of 150 or less (or both) was analyzed similarly. In the analysis of the time to remission, data on patients who were lost to follow-up were censored at the time of the last study visit and data on patients who were withdrawn from the study because of a deterioration in their condition were censored at 16 weeks.

RESULTS

A total of 182 patients were enrolled; 93 were randomly assigned to receive budesonide, and 89 were assigned to receive mesalamine. All patients took at least one dose of medication. The base-line charac-

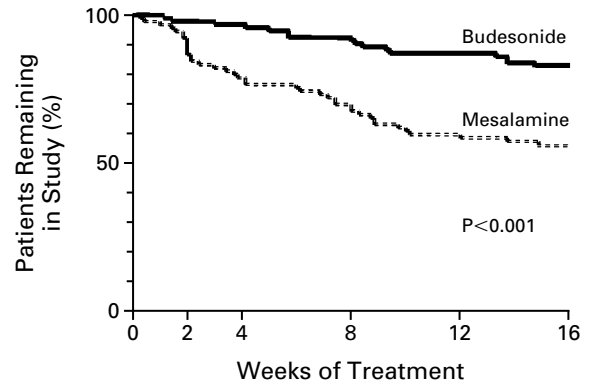
TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	BUDESONIDE GROUP (N=93)	MESALAMINE GROUP (N=89)
Sex (M/F)	30/63	28/61
Age (yr)		
Median	34	31
Range	19-74	18-67
Height (cm)		
Median	164	167
Range	150-190	148-194
Weight (kg)		
Median	60	60
Range	37-114	39-96
Crohn's Disease Activity Index		
Median score	266	278
Range	166-398	193-394
Duration of disease (yr)		
Median	6.1	4.6
Range	0-34	0-24
Duration of current exacerbation (mo)		
Median	1.8	2.0
Range	0-47	0-53
Disease site (no. of patients)		
Ileum	56	50
Colon	1	4
Ileum and colon	36	35
Previous intestinal resection (no. of patients)	35	37
Time since resection (yr)		
Median	3.7	4.5
Range	0-14	0-15
Length of resection (cm)		
Median	30	35
Range	10-100	10-95
Previous use of mesalamine (no. of patients)	27	31

teristics of the two groups of patients were similar (Table 1). Seventy-seven patients (83 percent) in the budesonide group and 50 patients (56 percent) in the mesalamine group ($P<0.001$) completed the scheduled 16 weeks of treatment and follow-up (Fig. 1). Worsening Crohn's disease led to the withdrawal of 10 patients in the budesonide group and 27 in the mesalamine group. Adverse events led to the withdrawal of three patients in the budesonide group and eight patients in the mesalamine group. Three patients in the budesonide group declined to continue the study. In the mesalamine group, two patients were found to be ineligible after randomization, one patient was lost to follow-up, and one was noncompliant. The mean length of treatment was 104 days in the budesonide group and 80 days in the mesalamine group ($P<0.001$). The results were very similar whether the data were analyzed according to the intention to treat or per protocol.

Clinical Efficacy

The rates of remission were higher in the budesonide group than in the mesalamine group throughout the study. The respective rates were 69 percent



NO. OF PATIENTS

Budesonide	93	91	89	86	81	77
Mesalamine	89	83	70	62	53	50

Figure 1. Proportions of Patients with Crohn's Disease Who Completed the Study.

The number of patients remaining in the study is shown below the graph.

and 45 percent ($P=0.001$) after 8 weeks, 64 percent and 42 percent ($P=0.004$) after 12 weeks, and 62 percent and 36 percent ($P<0.001$) after 16 weeks (Fig. 2). Disease activity was not assessed during treatment in two patients in the budesonide group and six patients in the mesalamine group, and thus, these patients could not be included in the analysis of remission. The median time to remission was also shorter in the budesonide group than in the mesalamine group (28 vs. 84 days, $P=0.04$).

Sex, previous intestinal resection, and previous use of mesalamine had no influence on the remission rates. In both groups, the rates of remission were lower among patients with more severe disease at entry (Crohn's Disease Activity Index, 301 to 400), but budesonide was still more effective. After 16 weeks, the remission rate was 41 percent among the 27 patients in the budesonide group with more severe disease and 11 percent among the 28 patients in the mesalamine group with more severe disease ($P=0.001$). The rates of remission were also lower among patients who also had colonic involvement. After 16 weeks the rate was 56 percent among the 37 patients in the budesonide group who also had colonic involvement and 23 percent among the 39 patients in the mesalamine group with such involvement ($P<0.001$).

Seventy-one percent of patients in the budesonide group had a decrease in the Crohn's Disease Activity Index of at least 100 points or a score of 150 or less after 16 weeks, or both, as compared with 51 percent of patients in the mesalamine group ($P=0.005$). These data are based on all patients, regardless of the disease site.

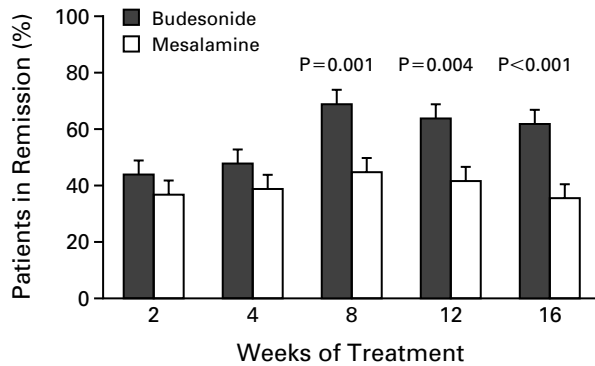


Figure 2. Mean (\pm SE) Rates of Remission among 91 Patients in the Budesonide Group and 83 Patients in the Mesalamine Group. For the analysis at two weeks, data were available for only 89 patients in the budesonide group.

Scores on the Psychological General Well-Being index after 16 weeks had improved significantly more in the budesonide group than in the mesalamine group (mean increase in total score, 23 vs. 14; $P=0.05$). Scores on all six subscales of the index (anxiety, depressed mood, positive well-being, self-control, general health, and vitality) showed the same pattern of improvement, with larger increases in the budesonide group, in particular after 12 and 16 weeks of treatment. There were no clinically significant changes in hematologic and biochemical variables in either group.

Adverse Events

The numbers of patients with adverse events were similar in the two groups; the most frequent events are shown in Table 2. Serious adverse events ($P=0.16$) and severe adverse events ($P=0.04$) were more frequent in the mesalamine group. All serious adverse events resulted in hospitalization. Only one serious adverse event in each group was considered to be possibly related to treatment: aggressive behavior in the budesonide group and fever in the mesalamine group.

Adrenal Function

Among the 76 patients who completed 16 weeks of treatment with budesonide and in whom adrenal function was assessed, the mean (\pm SD) morning plasma cortisol concentration was $11.3 \pm 7.3 \mu\text{g}$ per deciliter (312 ± 201 nmol per liter); the corresponding value for the 46 patients who completed 16 weeks of mesalamine therapy was $15.3 \pm 7.9 \mu\text{g}$ per deciliter (422 ± 218 nmol per liter). The peak value after stimulation with cosyntropin was $23.3 \pm 9.8 \mu\text{g}$ per deciliter (643 ± 270 nmol per liter) in the budesonide group and $35.9 \pm 15.2 \mu\text{g}$ per deciliter (991 ± 420 nmol per liter) in the mesalamine group. Sixty-seven percent of budesonide-treated patients and 83 per-

TABLE 2. ADVERSE EVENTS IN THE TWO TREATMENT GROUPS.

VARIABLE	BUDESONIDE GROUP (N=93)	MESALAMINE GROUP (N=89)
No. of adverse events	157	159
No. of patients with adverse events	59	64
No. of patients with serious adverse events	11	17
No. of patients with severe adverse events	12	22
Most frequent adverse events (no. of events)		
Headache	17	11
Abdominal pain	2	10
Enteritis	5	5
Nausea	3	7
Back pain	4	5
Dizziness	3	5
Vomiting	2	6
Anemia	3	4
Depression	4	3
Flatulence	2	5

cent of mesalamine-treated patients had normal plasma cortisol values before the cosyntropin challenge ($P=0.06$). Ninety percent of the budesonide-treated patients and 100 percent of the mesalamine-treated patients had normal increases in cortisol in response to cosyntropin ($P=0.02$).

DISCUSSION

We found that slow-release budesonide capsules were more effective than slow-release mesalamine tablets in inducing remission in patients with mildly to moderately active Crohn's disease of the ileum or the ascending colon (or both). Sex, previous intestinal resection, and previous use of mesalamine did not influence the remission rates.

The condition of patients in both groups improved after two weeks of treatment and reached a plateau after eight weeks. The degree of improvement was greater in the budesonide group. In a study comparing methylprednisolone with mesalamine,¹⁴ the results for methylprednisolone were similar to ours for budesonide. Budesonide has fewer side effects than systemic glucocorticoids such as prednisolone.^{5,6}

Some patients who received budesonide had impaired adrenal function, as assessed by a cosyntropin stimulation test, but the clinical significance of this finding is not known. Typical glucocorticoid-related side effects (such as moon face, hirsutism, and acne) were not among the most frequently reported adverse events in either treatment group. Both compounds were well tolerated, and the higher rate of severe adverse events and serious adverse events in

the mesalamine group may relate in part to the lower efficacy of this medication.

The 9-mg dose of budesonide was safe and effective, as has been found in previous studies.^{4,5} The results with the use of the 4-g dose of mesalamine were in accordance with data from a previous study,⁷ in which the remission rate was 43 percent and the mean score on the Crohn's Disease Activity Index decreased by 72 points 16 weeks after the start of treatment (the corresponding figures in our study were 36 percent and 76 points).⁷ However, neither a 4-g dose¹⁰ nor a 1.5-g dose⁸ of mesalamine was shown to be superior to placebo in other studies, nor was a 2-g dose effective against active Crohn's disease.¹⁴ We did not include a placebo group in our study, but remission rates of 18 to 35 percent have been reported with placebo in patients with active Crohn's disease.^{4,7-9}

Ethical principles of biomedical research require that patients be withdrawn from a controlled trial if their condition deteriorates substantially. Seventeen percent of the patients in the budesonide group and 44 percent of those in the mesalamine group did not complete the study. Approximately two thirds of the patients were withdrawn because of an insufficient therapeutic effect. These findings are similar to those in other studies.^{4,5,7} We did not collect data on the treatment the patients received after withdrawal.

The long-term effects of budesonide and mesalamine should be studied further, as well as the effect of higher doses of mesalamine. We studied a select group of patients with Crohn's disease of the ileum or ascending colon that was mild to moderately active, and the effect of these treatments in other groups of patients is not known. However, the therapeutic benefit of both drugs was less in patients with more active Crohn's disease and patients who also had colonic involvement.

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APPENDIX

In addition to the authors, the following persons and institutions participated in the International Budesonide-Mesalamine Study Group: *Odense University Hospital, Odense, Denmark* — K.

Lauritsen; *Hôpital Cochin, Paris* — S. Chaussade; *Rotherham District General Hospital, Rotherham, United Kingdom* — K. Bardhan; *Leigh Infirmary, Manchester, United Kingdom* — V. Mani; *Aker Sykehus, Oslo, Norway* — E. Aadland; *Università degli Studi di Bologna, Bologna, Italy* — C. Brignola; *Ospedale Nuovo Regina Margherita, Rome* — C. Prantera; *Hospital General Vall d'Hebron, Barcelona, Spain* — J.-R. Malagelada; *Hospital Germans Trias i Pujol, Badalona, Spain* — M. Gassull; *Instituto Português de Oncologia Francisco Gentil, Lisbon, Portugal* — F. Mira; *University Hospital of Heraklion, Heraklion, Greece* — O. Manoussos; *District General Hospital of Athens, Athens, Greece* — N. Skandalis; *Tygerberg Hospital, Cape Town, South Africa* — C. van Rensburg; *Johannesburg Hospital, Johannesburg, South Africa* — A. Mohamed; *Sozial Medizinisches Zentrum Ost, Vienna, Austria* — C. Sebesta; *St. Vincent's Hospital, Fitzroy, Australia* — W. Connell; *Royal Prince Alfred Hospital, Camperdown, Australia* — W. Selby; *Meath Hospital, Dublin, Ireland* — C. O'Morain; and *Astra Draco, Lund, Sweden* — I. Nylander.

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CORRECTION

A Comparison of Budesonide and Mesalamine for Active Crohn's Disease

A Comparison of Budesonide and Mesalamine for Active Crohn's Disease . On page 372, the sentence that begins on line 8 of the right-hand column should have read, "The median time to remission was also shorter in the budesonide group than in the mesalamine group (28 vs. 58 days, $P=0.12$)," not "(28 vs. 84 days, $P=0.04$)." as printed.