Budesonide in Collagenous Colitis: A Double-Blind Placebo-Controlled Trial With Histologic Follow-Up

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Background & Aims: Collagenous colitis (CC) is a well-described entity causing chronic diarrhea and characteristic histologic findings. Several treatment options have been suggested, but no controlled data are available. We conducted a placebo-controlled trial to show the clinical and histologic effects of budesonide in CC.

Methods: Twenty-eight patients were randomly assigned to receive placebo (n = 14) or budesonide 9 mg daily (n = 14) for 8 weeks. Patients were evaluated clinically, and blinded biopsy specimens were analyzed from fixed locations at weeks 0 and 8. Clinical response was defined as a decrease of at least 50% in the disease activity score (number of bowel movements in the last 7 days). At week 8, nonresponders received open-label budesonide for the next 8-week period; responders discontinued treatment and were followed up.

Results: Three patients discontinued the study prematurely. Intention-to-treat analysis showed clinical response in 8 of 14 patients in the budesonide group compared with 3 of 14 responders for placebo (P = 0.05) after 8 weeks of blinded therapy, together with improved stool consistency. Histologically, there was no change in the mean thickness of the collagen band but a significant decrease of the lamina propria infiltrate in the budesonide group (P < 0.001).

Conclusions: Budesonide is efficacious in inducing short-term clinical response in CC with significant reduction of the histologic infiltrate in the lamina propria.

Collagenous colitis (CC) is a chronic idiopathic inflammatory bowel disease of unknown origin. The disease has been well described in recent years; the diagnostic criteria are established and uniformly accepted. Main criteria include a (near) normal endoscopic appearance of the colonic mucosa, and a characteristic thickening of the subepithelial collagen band along with a dense lymphoplasmocytic infiltrate in the lamina propria on colonic biopsy. The disease affects predominantly women with a mean age of 65 at diagnosis. Patients sometimes have debilitating chronic diarrhea. The natural history of the disease is often chronic, although spontaneous remissions and relapses have been described.1–3

A variety of medical and dietary treatments have been tried in this condition. No single treatment was found to be uniformly active. Clinical responses have been described on different anti-inflammatory treatments retrospectively in small numbers of patients.4 Encouraging results have been reported using open-label bismuth subsalicylate in a small series of both collagenous and lymphocytic colitis patients.5,6 No larger prospective randomized double-blind studies have been published in the treatment of CC. Although the symptoms may fluctuate with or without anti-inflammatory treatment, histologic responses are rare.

Recently, the use of oral budesonide has been reported in the treatment of CC, showing promising results. However, patient numbers were limited and data uncontrolled.7,8

In a prospective controlled way, the present study aims to document the short-term clinical and histologic effects of budesonide in the treatment of CC.

Materials and Methods

Study Design

This prospective, double-blind, placebo-controlled clinical trial was conducted at Belgian universities and large peripheral centers. The protocol was approved by the institutional review boards of each collaborating investigator. Written informed consent was obtained from all patients.

Patients were equally randomized (1:1) to one dose of 9 mg budesonide daily (3 Budenofalk [BF] 3-mg capsules with pH-modified release; Dr. Falk Pharma, Freiburg, Germany) or
3 capsules of placebo. After 8 weeks of therapy and without breaking the randomization code, patients were evaluated for clinical response. Therapy was discontinued in responders; nonresponders received open-label BF therapy for the next 8 weeks. All patients were followed up for the full 16-week study period.

**Patient Populations**

The patient population included both newly recruited cases and cases diagnosed earlier in our retrospective series. All patients had established CC with chronic symptoms for at least 8 weeks and fulfilled the following diagnostic inclusion criteria.

**Clinical criteria.** For at least 2 months, presence of chronic watery diarrhea defined as at least 3 semi-loose or loose stools per day; no other significant cause for diarrhea on history and full clinical examination; negative stool examination for pathogens, parasites, and *Clostridium difficile* toxin.

**Endoscopic criteria.** A full colonoscopy (preferably with ileoscopy) was performed showing no obvious signs of macroscopic inflammation. Except for diverticulosis or diminutive polyop(s) no significant other findings were accepted.

**Histologic criteria.** The diagnosis of CC was made when the subepithelial collagen band on a well-oriented section of the mucosa had the typical feathery appearance of the inferior border and exceeded 10 μm. In addition, an increased mixed inflammatory cell infiltrate in the predominantly mononuclear lamina propria should be present. Other findings may include regenerative epithelial changes with mucus depletion, surface epithelial damage and sloughing, rare infiltration of neutrophils and eosinophils both in the epithelium and the lamina propria, but were not required for the diagnosis. Cases with overlapping histologic features with lymphocytic colitis (increased number of intraepithelial lymphocytes) were classified according to the most predominant findings. Overlap syndromes were therefore allowed if the collagen band was a predominant finding.

Medications that could possibly affect the stool frequency or the natural course of the disease were not allowed during the study period and discontinued before inclusion. An appropriate wash-out period was respected: 1 week for antidiarrheals (loperamide, cholestyramine) and anticholinergics; 2 weeks for aminosalicylates (mesalamine, sulphasalazine) and antibiotics; 4 weeks for corticosteroids; 4 weeks for any drugs known to potentially trigger the disease (nonsteroidal anti-inflammatory drugs [NSAIDs], ticlopidine [Ticlid; Sanofi Synthelabo, Paris, France], flutamide [Eulexin; Schering Plough, Kenilworth, NJ], ranitidine, herbs); and 3 months for azathioprine and other immunosuppressives.

Other chronic medications (e.g., antihypertensives, benzodiazepines) were allowed to be continued as long as the intake remained stable throughout the entire study period. The use of aspirin or NSAIDs was not allowed except for a prophylactic (cardiac) aspirin dose.

Patients with associated significant gastrointestinal disease (except for patients with controlled gastroesophageal reflux disease and celiac disease strictly adhering to their diet for years) were excluded from the trial. Patients were not allowed to take any antidiarrheal agents and consented to regular follow-up.

**Colonoscopy and Biopsy Procedures**

In all patients, diagnosis was previously confirmed by a full colonoscopy with at least 5 random biopsies from different colonic segments; biopsies were read by the local pathologist. Before inclusion, 4 biopsies were obtained (2 from the rectosigmoid junction [15 cm from the anal verge] and 2 from the sigmoid [25 cm]) during the diagnostic colonoscopy, or by sigmoidoscopy for patients with a previously established diagnosis of CC. Four repeat biopsies from the same locations were obtained at week 8. All biopsies were randomly read by 2 blinded expert pathologists (K.G. and F.D.). Initial diagnosis was confirmed in all cases. Histologic analysis consisted of the evaluation of the thickness of the collagen band (measured as the mean thickness on the well-oriented section), the degree of infiltration in the lamina propria, and the number of intraepithelial lymphocytes. The infiltrate of the lamina propria was scored semiquantitatively as normal, slightly increased, or dense.

**Evaluations**

All subjects kept a diary throughout the 16-week study period. In the diaries they recorded daily the number of stools; abdominal pain, bloating, and general well-being were scored on a 3-point scale. At weeks 2, 0, 2, 4, 8, 12, and 16 patients were evaluated clinically, diaries were collected, side effects recorded, compliance with study medication was checked, and intake of concomitant drugs registered. Sigmoidoscopy with biopsies from fixed locations was performed at weeks 0 and 8.

**End Points and Definitions**

Disease activity score was defined as the number of bowel movements in the last 7 days before the evaluation visit. Clinical response was defined as a decrease of at least 50% in the disease activity score at week 8 compared with week 0. Histologic response was defined as a statistically significant reduction of the infiltrate in the lamina propria and/or a significant reduction in the mean thickness of the collagen band.

Primary end points of the study were the number of clinical responders and the number of histologic responses at week 8 in the active treatment group compared with placebo.

Secondary end points were the impact on abdominal pain, stool consistency score, and the patient’s general well-being, the time necessary to induce remission, and the safety and long-term clinical effects of budesonide including the relapse rates after weaning or discontinuing budesonide.
Statistical analysis. Given the low incidence of CC, sample size calculations were based on a cohort of 30 patients. For 30 patients (2 × 15) a statistical power of 45.8% was calculated to obtain a significant difference considering: a response rate in the placebo group of 20% and a response rate of 60% in the active treatment group. All calculations were made on an intention-to-treat basis using the \( \chi^2 \) test for dichotomous variables to compare means of different groups and the nonparametric Wilcoxon test to compare the means in the same group.

Open-Label Follow-up

Compassionate-need budesonide was allowed to all patients responding to BF who had a subsequent relapse on discontinuation of the drug. Compassionate-need requirements were recorded per patient.

Results

A total of 28 (20 females) patients were randomized to placebo (n = 14) or 9 mg BF (n = 14) for an initial 8-week period. Both groups were equally distributed for baseline characteristics including age, sex, median duration of disease, medication use, and associated autoimmune conditions (Table 1). Three patients dropped out of the study (2 placebo), one for noncompliance and 2 because of treatment failure.

Primary Endpoints

Clinical. Intention-to-treat analysis showed, according to our stringent definition of clinical response, 8 of 14 responders in the budesonide group compared with 3 of 14 in the placebo group at week 8 (\( P = 0.05 \)). As shown in Figure 1, the maximal clinical effects were already reached at the first time point of evaluation (week 2) and were maintained throughout the 8-week study period. Of the remaining 6 patients who did not respond to active treatment, 2 more patients had a favorable outcome that was considered as a clinical response by themselves and their physicians; however, this outcome did not meet our more stringent criterion for clinical response. The disagreement can be explained by the low baseline disease activity scores of some patients. If we exclude the patients (3 budesonide, 2 placebo) who did not reach the entry criterion of a minimum of 21 stools per week at week 0, 8 of 11 budesonide patients responded, and 3 of 12 placebo patients (\( P = 0.02 \)) responded.

Histologic. The central blinded histologic analysis of biopsies showed distinct effects after 8 weeks of therapy compared with baseline (Table 2). In the budesonide group, all patients had a significant reduction of the infiltrate in the lamina propria (9 of 13 patients showed a complete normalization of the infiltrate in the lamina propria, and the remaining 4 showed a partial response). In the placebo group, 4 of 12 showed a partial response, whereas 8 of 12 showed no response at all (\( P < 0.001 \)). In terms of the thickness of the subepithelial collagen band there were no significant differences between both groups although a remarkable reduction was

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<th>Table 2. Histologic Results of Lamina Propria Infiltrate</th>
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\(^a\)Response was defined as a normalization of the infiltrate in the lamina propria at week 8 compared with week 0.
found in a subset of patients in the active treatment group, as well as in 3 placebo patients (Figures 2 and 3).

Secondary Endpoints

In addition to the number of bowel movements, patients recorded daily stool consistency, bloating, abdominal pain, and general well-being on a 3-point scale. At each follow-up visit, average scores were calculated based on patients’ diaries of the preceding 7-day period. Statistically significant improvement was observed for average stool consistency at week 4 for budesonide compared with placebo ($P < 0.05$). No significant differences were found for the other variables (abdominal pain, bloating, and general well-being) (Figure 4).

Follow-up After Week 8

Nine of 11 placebo nonresponders were switched to 8 weeks of open-label budesonide. A complete response (according to the same stringent definition) was found in 7 of 9 patients, partial response in 1 of 9 patients, and dropout in 1 of 9. In the subgroup of patients responding or asking for open-label compassionate-need budesonide (10 during the blinded and 9 in the open-label phase of the trial) 7 of 19 (37%) could discontinue therapy after the first 8-week period, whereas 12 of 19 (63%) required further treatment beyond the
8-week period for at least 1 additional month because of clinical relapse. This clinical relapse could not be predicted based on the baseline or follow-up histopathologic examination.

Safety. One patient in the placebo group was hospitalized for depression at week 4. No serious adverse event related to the study medication was observed throughout the study. Only minor events were noted, almost equally distributed in both groups. Most common side effects included viral infection (n = 3), rash (n = 2), hypertension (n = 1), and slight Cushingoid face (n = 3).

Discussion

This is the first randomized placebo-controlled clinical trial for the treatment of CC. All other reported series were smaller, uncontrolled, and often included cases with lymphocytic colitis. Although the open-label clinical effects were quite convincing for budesonide, both in reported series and in our own experience, the results of this study are somewhat more moderate. A number of patients in the budesonide group did not achieve remission, and we observed remarkable clinical and near histologic remission in 3 patients in the placebo group. Some patients showed an important improvement in the number of weekly stools, which was probably linked to the low bowel movement scores at baseline, although the intended 50% reduction could not be reached. This study underlines once again the importance of placebo-controlled trials. Placebo responses are quite high and spontaneous remissions occur.

The histologic effects were more pronounced in favor of the active treatment group. There was marked improvement or normalization of the infiltrate in the lamina propria in all patients on budesonide. A clear reduction in the mean collagen band thickness was observed in only a few patients. These data are perfectly in concordance with the literature describing clinical efficacy of a number of agents but rare histologic remissions, as far as the collagen band is concerned. Perhaps the disappearance of the collagen band may take more time. The relatively moderate decrease of the collagen band depicted in Figure 3 is caused by the location of the biopsies. For diagnosis, random biopsies from all segments of the colon were obtained, whereas for comparison in the study mean thickness from the rectal (15 cm) and sigmoid (25 cm) location was used. Detailed histopathologic studies comparing the different colonic segments showed marked subepithelial thickening in the right colon and a less pronounced collagen band in the rectum and distal sigmoid. For practical and ethical reasons, we used only sigmoidoscopic examinations for follow-up examinations.

Classic corticosteroids have been used in the treatment of CC with variable success. Although debilitating in some patients, the benign course of the condition does not justify the prolonged use of these agents. Better responses for budesonide have been reported even in patients refractory to systemic steroids. This can be explained by the higher topical activity caused by superior binding to the glucocorticosteroid receptor. Although the coated budesonide capsules (Dr. Falk Pharma preparation) are designed to release budesonide predominantly into the terminal ileum, sufficient concentrations of the active substance can be achieved in the transverse to left colon to realize a local effect.

In all patients, clinical effects were observed within the first 2 weeks and were maintained throughout the study period. About one third of patients could discontinue budesonide treatment after the initial 8-week study period, but two thirds asked for open-label continued treatment for an extra 1 to 5 months. We treated them as an on-demand compassionate-need basis with 6 mg of budesonide daily. At the completion of the trial, budesonide could be discontinued in all but 2 patients. Even after longer-term treatment, no significant toxicity was observed.

Although microscopic colitis is still an idiopathic condition, a significant proportion may be drug-induced. At the time of the design of this study, all medications known to induce collagenous or lymphocytic colitis were discontinued. Later, we became aware that some patients may have developed their condition after starting a proton pump inhibitor. Seven patients were taking a proton pump inhibitor at diagnosis (5 lansoprazole, 2 omeprazole). In 6 of 7 patients, the start of drug therapy preceded the onset of symptoms for a median of 5 months. Lansoprazole was stopped spontaneously by one patient 2 months before inclusion because he thought it caused diarrhea. Drug therapy was contin-
ued in the other patients. The high incidence of patients on proton pump inhibitors (especially lansoprazole) suggests a link, but in the absence of further study, it is impossible to prove a relationship between the proton pump inhibitor and the development of CC.

In terms of therapeutic alternatives, remarkable open-label responses have been described for bismuth subsalicylate. Although readily available in the United States, this compound is not available in many countries throughout Europe. There is some concern about central nervous toxicity of long-term use of these agents. The reported series also included patients with lymphocytic colitis. The latter is more likely to be drug-induced, and early spontaneous remissions are more frequent. Moreover, bismuth, as well as steroid components, may have nonspecific antidiarrheal effects. These questions may be resolved by a larger controlled trial using bismuth in a homogeneous group of CC patients, and such a trial was announced.

We previously used open-label budesonide in lymphocytic colitis. The experience from the reported case was confirmed in approximately 20 patients. Usually the response is quite dramatic early on and sustained when discontinuing the drug after 2 weeks.

**Conclusions**

Budesonide is efficacious at inducing short-term clinical and histologic responses in patients with CC. In routine practice, we will carefully exclude drug-induced cases and wait temporarily for possible spontaneous remissions using nonspecific antidiarrheal agents. In patients with refractory disease or severe symptoms, we will use budesonide for 1 to several months on an on-demand basis.

**References**


