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Budesonide in the Treatment of Refractory Celiac Disease

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OBJECTIVE: Corticosteroids are used in patients with refractory celiac disease. In order to minimize their systemic side effects, we assessed the role of a locally active sustained release corticosteroid with minimal systemic bioavailability in patients with refractory celiac disease in an open labeled noncontrolled study.

METHODS: Patients who received budesonide for refractory celiac disease were classified according to whether they were primarily or secondarily unresponsive to the diet, and whether they had a polyclonal (type I) or clonal (type II) expansion of intraepithelial lymphocytes. The response to budesonide was assessed globally and by reduction in bowel movements.

RESULTS: Patients (N = 29, 72% female) received budesonide for a mean of 6.7 ± 8.5 months, 5 patients (18%) had type II disease (clonal T-cell population); 76% responded to the medication, 55% completely. Response occurred when budesonide was used alone or with oral corticosteroids and/or azathioprine. There was an objective improvement in the number of bowel movements in those that responded. Response occurred in those with either primary or secondary refractory disease and in those with type II disease, irrespective of the presence of microscopic colitis (N = 7). There was no improvement in the duodenal biopsy over the study period and there were no side effects of budesonide.

CONCLUSIONS: Budesonide may be of value in the management of refractory celiac disease.

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INTRODUCTION

Celiac disease is an autoimmune enteropathy triggered by ingestion of gluten, the storage protein of wheat, and similar proteins in rye and barley (1). A gluten-free diet is the mainstay of treatment; however, up to 7–30% of patients have poor responses to this dietary therapy (2–4). While a systematic approach to the evaluation of these patients frequently reveals a treatable cause for this poorly responsive state, no other disease process is discovered in some patients (1–5). These poorly responsive patients with persistent symptoms and villous atrophy on biopsy, despite adherence to a gluten-free diet for at least 6–12 months, are determined to have refractory celiac disease (4, 6). Patients with refractory celiac disease are classified as having either primary refractory disease if they never responded to a gluten-free diet or secondary if their disease relapsed, despite adherence to the diet (4). An alternate classification is based on determining the presence of clonal proliferations of intraepithelial lymphocytes that have phenotypic aberrations (6).

Corticosteroids, either alone or in combination with other immunosuppressive drugs, are used in refractory patients, especially those with severe persistent or recurrent symptoms despite being on a strict gluten-free diet (3, 6–10); their use is however limited by systemic side effects. Topically active steroids are therefore attractive for treating patients who have poorly responsive or refractory celiac disease, since they have low systemic bioavailability and provide immunosuppressant activity in the bowel, avoiding deleterious systemic effects.

Budesonide is a synthetic steroid that has high topical glucocorticoid activity, but low systemic bioavailability because of high first-pass metabolism primarily by cytochrome P450 in the liver (2, 11). Entocort EC (controlled-release budesonide) is enteric coated and is designed to deliver the active drug to the distal small intestine and colon (2, 11). However, studies have revealed that about 30% is released and absorbed in the upper small intestine (2, 11). We therefore evaluated the use of this drug in refractory patients who were compliant with a gluten-free diet.

METHODS

Patients with celiac disease responding poorly to dietary restriction of gluten, and in whom budesonide was prescribed, were identified from the database of our university based celiac disease center. An experienced dietician assessed dietary compliance, and patients noncompliant to the diet

were excluded. Data regarding patient's demographics, mode of disease presentation, serology profiles (endomysial antibody [EMA] and/or tissue transglutaminase antibody [tTG]), dose and duration of budesonide use, clinical response, and concomitant medication use were recorded. All poorly responsive patients had undergone extensive evaluation that included colonoscopy and colon biopsies, CT scans of the abdomen and pelvis, imaging of the small intestine either by small bowel series or video capsule endoscopy, and stool specimens were examined for ova and parasites and breath tests performed to exclude bacterial overgrowth. Antijejunal antibodies, used to exclude autoimmune enteropathy, were performed in one patient. Patients had received pancreatic supplements, bismuth, and antibiotics prior to the use of steroid or immunosuppressants. This study was approved by our institutional review board.

Mode of presentation, at the time of initial celiac disease diagnosis, was classified as classical (diarrhea predominant) and atypical (absence of diarrhea). Unresponsiveness to the diet was classified as primary (no response to gluten-free diet to begin with) or secondary (recurrence of symptoms after initial response to diet) (4). Based on the results of polymerase chain reaction (PCR) analysis for T-cell receptor gene (TCR) rearrangement, the cohort was also divided into two groups; type I refractory celiac disease if TCR gene rearrangement analysis yielded a polyclonal product and refractory celiac disease type II if the TCR gene rearrangement was clonal (6).

Budesonide treatment outcomes were globally classified as complete response, moderate response, and poor response, a modified form of scale used by Chopra *et al*. (25) for inflammatory bowel disease patients (Table 1). The global assessment was based on the patient claiming that they were improved with loss of systemic symptoms such as fatigue and increased well-being as well as the physician's assessment of both the laboratory and clinical data. In order to assess the response objectively, the number of bowel movements for subjects with classical presentation and body mass index (BMI) for all subjects were recorded before and after budesonide treatment. The change in BMI was assessed using paired samples *t*-test.

Duodenal biopsies for all patients were reviewed and degree of villous atrophy was classified as partial (PVA), subtotal (STVA), or total (TVA). Cases with subtotal and total villous atrophy were combined together (denoted as TVA) for this study. Histopathology was compared before and after budesonide treatment. PCR analysis for TCR gene rearrangement was performed on formalin-fixed paraffin-embedded small bowel biopsies followed by polyacrylamide gel electrophoresis and heteroduplex analysis (13).

Table 1. Classification of Budesonide Treatment Outcome

Complete response	Resolution of symptoms in patients completely weaned off systemic steroids
Moderate response	Resolution of symptoms and systemic steroid dose reduction
Poor response	Persistent symptoms despite therapy

RESULTS

A total of 30 refractory celiac disease patients received budesonide between January 2000 and April 2005, one patient was excluded from the study because she did not come for a follow-up visit. Twenty-four patients were on a gluten-free diet for at least 6 months, while 5 patients were on the diet for less than 6 months, each of the latter group of patients had required hospitalization because of severe disease manifestations. Patient demographics along with histopathology and serology results are shown in Table 2. All 29 patients fulfilled the criteria for celiac disease with compatible biopsies and serologic profiles. Only one patient with negative endomysial antibodies had antijejunal antibodies assessed, they were negative. Our cohort was female predominant (72%) and more patients had a classical (90%) compared with atypical (10%) presentation. Unresponsiveness to gluten-free diet was primary in 55% and secondary in 45% of the patients. All patients had persistent villous atrophy and intraepithelial lymphocytosis despite the diet. The degree of villous atrophy was partial in 69% and total in 31%. Antibodies to EMA and/or tTG were positive in 31% at the time of assessment of the refractory state, despite strict adherence to the diet. These patients had been on the diet for less than 12 months. All serological tests became negative during the period of this study. PCR for TCR-γ gene rearrangement was performed in all except one patient; 23 patients (82%) had type I refractory celiac disease (polyclonal) and 5 patients (18%) had type II disease (clonal).

Mean age at the start of budesonide therapy was 56 yr, and all patients except 5 had celiac disease for at least 6 months' duration (range 1–249 months) (Table 2). All patients received 9 mg of budesonide per day and it was used for a mean of 7 months (range 1–36 months). During the time period of this study, one patient with type II refractory celiac disease died of sepsis and malnutrition.

Table 2. Demographic Characteristics (N = 29)

		%
Gender	Females	72
	Males	28
Presentation	Classical	90
	Atypical	10
Type of refractory state	Primary	55
	Secondary	45
Villous atrophy	PVA	69
	TVA	31
EMA or tTg	Positive	31
	Negative	69
Duration of CD	Mean ± SD (months)	60.9 ± 71.3
Age at budesonide start	Mean ± SD (years)	56.3 ± 15.4
Duration of budesonide use	Mean ± SD (months)	6.7 ± 8.5

CD = celiac disease; PVA = partial villous atrophy; TVA = total villous atrophy; EMA = endomysial antibody; tTG = transglutaminase antibody IgA.

Table 3. Budesonide and Concomitant Medication Use in Relation to Budesonide Response

Therapy	Number of Patients	Complete Response	Moderate Response	Poor Response
Budesonide alone	15	12		3
Budesonide + S	3	1	1	1
Budesonide + S + A	7		5	2
Budesonide + A	4	3		1
Total	29 (100%)	55%	21%	24%

S = systemic steroids; A = azathioprine.

Table 4. Number of Bowel Movements Before and After Budesonide Treatment

Patient Groups		Complete Response	Moderate Response	Poor Response
No. of bowel movements (mean ± SD)	Initial	6.3 ± 6.6	6.7 ± 6.5	5.5 ± 2.2
	Follow-up	1.2 ± 0.6	1.3 ± 0.5	5.5 ± 2.9

Use of immunomodulatory medications in addition to budesonide: the use of prednisone and azathioprine was based on the severity of symptoms. Some subjects received steroids or azathioprine before budesonide became available. The initial dosage of prednisone was 20–40 mg daily with efforts to taper the dosage as the patient responded. Azathioprine was used in an initial dosage of 50 mg daily; three patients received 75 mg daily. These therapies were used for a duration of 1–60 months (mean 9.6 months).

We looked at the use of budesonide along with concomitant systemic steroids and other immunomodulators in relation to the three outcome groups (Table 3). Overall, 76% of the patients had a response to budesonide, considered as complete response in 55%. The number of bowel movements in the subjects decreased from six to one in both the complete and moderate response groups, but it remained the same in the poor response group (Table 4). Overall, there was a slight improvement in BMI from 20.8 ± 3.9 to 21.1 ± 3.6, but this was not statistically significant ($P = 0.37$).

When budesonide was used without other immunomodulatory agents, 12 patients (80%) had a complete response and only 3 (20%) had a poor response. When budesonide was used with steroids, azathioprine, or both, a complete response was noted in 4, moderate in 6, and a poor response in 4 patients.

We also looked at the patient characteristics in relation to budesonide response Table 5. Among those with primary refractory celiac disease there was an almost equal distribution among the three outcome groups, whereas patients with secondary refractory disease had a complete response in 10 (77%), moderate response in 2 (15%), and poor response in one. Almost an equal percentage of patients with PVA (55%) and TVA (56%) had a complete clinical response. However, there was no noticeable improvement in the degree of villous atrophy in follow-up duodenal biopsies from any patient. Type II refractory patients had persistent clonal proliferation of IELs. Of the nine patients who had positive antibodies when assessed for the refractory state, a complete response was noted in 6 and poor response in 3 patients. Patients with both type I and II refractory disease responded to budesonide therapy.

Seven patients had concomitant microscopic colitis, 5 (71%) responded to budesonide treatment (complete response in 3 and moderate response in 2). Six patients had lymphocytic colitis and one had collagenous colitis. The latter patient only had a moderate response to the therapy. No patient had side effects that could be attributed to budesonide treatment.

DISCUSSION

Corticosteroids are used in patients with celiac disease who are severely ill, despite a gluten-free diet. They may be used alone or along with immunomodulatory agents such as azathioprine (7, 9, 14–16), cyclosporine (15, 17), or inflixamab (18, 19). With an aim of minimizing the systemic side effects of corticosteroids, we assessed the role of a locally acting controlled-release corticosteroid, budesonide, in 29 patients with poorly responsive celiac disease. A beneficial clinical response to budesonide either used alone or in combination with systemic steroids or azathioprine was observed in 76% of patients. When budesonide was used in combination with oral steroids and/or azathioprine it is realized that all agents may have contributed to improvement in the patients' condition, including the effect of a delayed response to the azathioprine.

Several lines of evidence support the use of locally acting controlled-released corticosteroids in celiac disease. Firstly, celiac disease is a chronic inflammatory small intestinal disease that primarily involves the proximal small intestine, but may in some patients involve the entire small intestine (20–22). Entocort EC, with its release in the small intestine, allows delivery of a locally active corticosteroid preparation to the involved tissues (11, 12). Secondly, this class of drug has been previously been demonstrated to be efficacious in celiac disease. Mitchison *et al*. and Bramble *et al*. used topically active corticosteroids in patients with celiac disease while on a regular diet. Improvement in both histology and parameters of absorption was noted (23, 24).

Experience of the use of budesonide in celiac disease is, however, limited. There had been no reports of its use when we started this study. Subsequently, in a study of budesonide use for inflammatory bowel disease, Chopra *et al*. (25) mentioned that the drug was used in two patients with celiac disease, without obvious benefit. The clinical details of these patients were not included. However, in another study the drug was considered beneficial in patients with refractory sprue syndromes, including 7 with refractory celiac disease, one with autoimmune enteropathy, and another with enteropathy

Table 5. Distribution of Subjects' Characteristics in Relation to Budesonide Response

		Complete Response (%)	Moderate Response (%)	Poor Response (%)
Lack of response to GFD	Primary (16)	37.5	25	37.5
	Secondary (13)	77	15	8
Presentation	Classical (26)	54	23	23
	Atypical (3)	67	0	33
Villous atrophy	PVA (20)	55	15	30
	TVA (9)	56	33	11
EMA or tTG antibodies	Positive (9)	67	0	33
	Negative (20)	50	30	20
TCR-γ gene rearrangement	Clonal 5	60	20	20
	Polyclonal 23	52	22	26

CD = celiac disease; GFD = gluten-free diet; PVA = partial villous atrophy; TVA = total villous atrophy; EMA = endomysial antibody; tTG = transglutaminase antibody IgA; TCR = T-cell receptor gene rearrangements.

associated T-cell lymphoma (26). We used the method of assessing the response to budesonide that had been developed by Chopra *et al*. at the Mayo Clinic (25), fully aware that this had been used to assess patients with inflammatory bowel disease. There is no currently published tool for assessing the severity of illness for patients with celiac disease.

Type II refractory celiac disease, as ascertained by the presence of clonally expanded intraepithelial lymphocytes, presents a difficult management problem. Patients typically have a very difficult course, receive immunosuppression, and often deteriorate despite treatment (27). This was seen in one of our patients with type II refractory disease who died of sepsis and malnutrition during the period of this study. Patients with type II refractory disease are also at an increased risk for the development of lymphoma (9). However, we noted improvement in 4 of 5 patients with type II refractory celiac disease with the administration of budesonide, supporting the observations of Daum *et al*. (26).

Overall, despite improvement in clinical symptoms, there was no change in the duodenal histology on treatment with budesonide. This is probably related to the major site of action being the more distal small bowel as well as the fact that morphological improvement in duodenal biopsies lags behind clinical improvement (29).

Seven of the patients had concomitant lymphocytic colitis, an indication in itself for budesonide use (30). The majority of these patients did well on budesonide. However, when we excluded patients with microscopic colitis from the overall analysis, 77% of patients without microscopic colitis benefited from budesonide therapy. Budesonide is therefore of value in the treatment of celiac disease irrespective of coexistent microscopic colitis.

The major limitation of our study is that it is uncontrolled, without a placebo arm. Despite this, the analysis of response to the drug suggests that budesonide is beneficial in patients with refractory celiac disease, both in individuals with primary or secondary unresponsiveness to the diet. In addition, the drug is beneficial in patients with type II refractory disease. This group, however, needs to be followed closely because of their poor long-term prognosis (6).

In view of the results demonstrated in this study a prospective placebo-controlled study is indicated. However, in the interim, we advocate the use of budesonide as first-line therapy in patients with celiac disease that require immunosuppressive or immunomodulatory drugs.

STUDY HIGHLIGHTS

What Is Current Knowledge

- 7–30% of patients with celiac disease have poor responses to a gluten-free diet.
- Corticosteroids/immunosuppressants are used in refractory patients.
- Systemic steroids are associated with systemic side effects.

What Is New Here

- Budesonide is useful in the management of refractory celiac disease.
- Response occurred in the presence of aberrant T-cell populations (type II refractory celiac disease) as well as in their absence (type 1).
- Response occurred irrespective of the presence of microscopic colitis.
- Budesonide can be used along with other immunomodulatory agents.
- Objective improvement in the number of bowel movements.
- No improvement in the duodenal biopsy over the study period.
- No side effects of budesonide.

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CONFLICT OF INTEREST

Guarantor of the article: Peter H.R. Green, M.D.
Specific author contributions: Dr. Peter H.R. Green is responsible for the entire contents. Dr. Pardeep Brar and Dr. Ikenna Egbuna are the fellows who analyzed and compiled the data. Dr. Susie Lee, Dr. Suzanne Lewis, and Dr. Peter H.R. Green looked after the patients, while Dr. Govind Bhagat is the pathologist involved in the study.
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