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Efficacy of Enteric-Release Oral Budesonide in Treatment of Acute Reactions to Gluten in Patients With Celiac Disease

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Introduction

Celiac disease (CeD) is a common gluten-responsive T-cell mediated enteropathy. The only current treatment is gluten avoidance; however, even when attempting to adhere to a gluten-free diet (GFD), symptomatic gluten exposures are frequent[1].

Budesonide is a corticosteroid with a high first-pass hepatic metabolism. Previous reports showed that budesonide may induce clinical and histologic response in refractory celiac disease (RCD)[2, 3]. Budesonide has been used also for the treatment of celiac crisis and as an adjuvant to the GFD at diagnosis[4, 5]. Here we describe the use of enteric-release budesonide to abort acute symptoms following inadvertent gluten ingestion.

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Methods

Retrospective case series of consecutive CeD patients at the Celiac Center at Beth Israel Deaconess Medical Center (BIDMC) with an acute gluten exposure treated with enteric-release budesonide. Cases were identified through a clinical query of electronic medical records. Patients with biopsy confirmed CeD or potential CeD [normal duodenal histology, elevated tissue transglutaminase antibodies (tTG), HLADQ2.5 or DQ8 positivity and clinical response to GFD] were included. Overall, patients were clinically well except for acute severe reactions after suspected accidental gluten exposure. Those presenting with celiac crisis[4], evaluated for non-responsive celiac disease, or receiving budesonide for microscopic colitis or for complicated CeD were excluded. The primary outcome was patient-reported clinical response to budesonide, defined in terms of symptom severity and duration as “substantial”, “response” and “partial” (Table 1). The BIDMC Institutional Review Board approved the study.

Results

We identified 13 cases (all women, Table 1). Median age at CeD diagnosis was 39 (range 15–62) years and median GFD duration was 2.7 (range 1–12) years. Twelve patients had biopsy-confirmed CeD; one had potential CeD (Table 1, case 7). Patients were offered a trial of budesonide therapy because of reported distress regarding severity and duration of symptoms following gluten exposure. Symptoms lasted from 2 days to 4 weeks with diarrhea, abdominal pain and nausea and/or vomiting being the most common. Enteric-release budesonide was initiated as soon as possible after gluten exposure and symptom onset. Initial dose was 9 mg daily for most patients (85%). The total treatment duration ranged from 3 to 28 days. All patients reported a clinical response to budesonide, including 8 patients (62%) with substantial improvement in GI symptoms. Most partial responses were related to extraintestinal manifestations (EIM). Two patients (15%) reported adverse events (headache and constipation). Nine patients (69%) took additional course(s) of budesonide, with all exhibiting clinical response. One patient who used budesonide on multiple occasions reported that it was most effective when taken at symptom onset.

Discussion

While budesonide has been used for various indications in celiac disease[2–5], to our knowledge, this is the first report of the efficacy of budesonide for treatment of acute symptoms of gluten exposure. We do not advocate steroid use for uncomplicated CeD; the patients included in this report were selected for a trial of budesonide because of severe, debilitating gluten reactions due to intermittent inadvertent exposures despite their best attempts to adhere to a GFD.

Budesonide is a micronized corticosteroid with high topical effect. It binds to the transcription factor NF-kB, blocking the transcription of pro-inflammatory genes, and also increases the expression of anti-inflammatory genes[6]. Direct anti-inflammatory effects on the intestinal mucosa challenged with gliadin have been shown[5], as well as inhibitory

actions on mast cells, eosinophils and T_H2 cells[6], all of which may have roles in acute symptoms in CeD[7, 8].

The topical effect and high first pass elimination of budesonide may explain the observed greater efficacy for gastrointestinal symptoms compared to EIM as the later may be related to systemic inflammation. Individuals with EIM may benefit from a longer taper (3 to 4 weeks) compared to those with predominantly GI symptoms (3–9 days taper). Alternatively, EIM may require systemic therapy or may have been unrelated to CeD. Short courses of budesonide were well-tolerated, seldom associated with any systemic steroid side-effects and several patients received multiple courses. Of note, a prolonged treatment regimen of 3 mg three times a day including two open-capsules to deliver the drug proximally has been proposed to be more efficacious for clinical and histologic improvement in RCD[2].

Although this retrospective study lacks objective endpoints and various treatment regimens were used, we report that budesonide may be an attractive option to mitigate acute flares of symptoms related to gluten exposures in celiac disease, justifying future clinical trials.

Abbreviations:

BIDMC	Beth Israel Deaconess Medical Center
CeD	Celiac disease
EIM	Extraintestinal manifestations
GFD	Gluten-free diet
RCD	Refractory celiac disease
tTG	tissue transglutaminase antibodies

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Table 1:

Clinical characteristics and budesonide treatment

Case	Age (years)	Sex	GFD Duration (years)	Symptoms[a]						Symptom Duration following acute gluten reaction	tTG (U/mL)[b]	Treatment duration and dosage:	Clinical Response[c]		Adverse events
				D	P	N/V	B	C	Extraintestinal manifestations				GI	Non-GI	
1	28	F	12	D		N/V			Fatigue, rash	2–3 weeks	Normal	3 days: 9 mg daily	Substantial		None
2	32	F	12	D	P	N/V			Fatigue, brain fog	1 week[d]	Normal		Substantial	Partial	None
3	18	F	3		P	N/V			Fatigue, Headaches	2 days	< 1 × ULN[e]	3 days: 6mg, 6mg, 3mg	Substantial		None
4	64	F	2	D	P	N/V			Headaches, flushing	Few days	Normal	9 days: 9mg/3d, 6 mg/3d, 3 mg/3d	Substantial		None
5	50	F	1	D	P	N/V			Fatigue	3 weeks	Unknown	10 days: 9mg daily	Substantial	No response	Headache
6	51	F	1		P		B		Brain fog, joint pain, ataxia	2 weeks	Normal	A few days: 9 mg daily until better	Response	Partial	None
7[f]	60	F	2		P	N/V	B	C	Fatigue, brain fog	2 weeks	Normal	3 weeks: 6 mg/2w, 3 mg/1w	Substantial	Partial for fatigue	None
8	41	F	11	D					None	1 week	<1 × ULN[g]	3 weeks: 9 mg/1w, 6 mg/1w, 3 mg/1w	Substantial	NA	None
9	43	F	4	D	P				None	Few weeks	Normal	3–4 weeks: 9 mg/1–2w, 6 mg/1w, 3 mg/1w	Response	NA	None
10	39	F	1.6	D	P	N/V	B		Fatigue, brain fog, joint pain	3–4 weeks	Normal		Partial		None
11	70	F	9	D					None	4 weeks	Normal		Substantial	NA	Constipation
12	56	F	2	D	P				None	2 days	Unknown		Response	NA	None
13	35	F	2.7		P	N/V			None	2 weeks	2 × ULN[g]	4 weeks: 9 mg daily	Partial	NA	None

F, Female; M, Male; D, Diarrhea; P, Abdominal pain; N/V, nausea and/or vomiting; B, Bloating; C, constipation; ULN, upper limit normal; w, week; d, day;

[a]Symptoms of acute gluten exposure were similar to symptoms at CeD diagnosis, with the exception of case 4 and 9 who were asymptomatic at diagnosis (screened because of family history of CeD or osteoporosis) and after following a GFD, developed symptoms if exposed to gluten;

[b]INOVA anti-human IgA TTG, borderline 20–30, positive >30;

[c]"Substantial" response: patient-reported substantial decrease in symptom severity and duration compared to previous gluten exposures; "partial" response: some degree of improvement in terms of severity, but not duration; "response": a clinical response was observed, but chart-review was insufficient to properly measure the extent of the response and effect on symptoms duration;

[d]Mostly non-GI symptoms, GI symptoms last about two days;

[e]Patient was exposed several times at the college cafeteria before starting budesonide;

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[f] Potential CeD;

[g] Previously not strictly adherent to a GFD, but were on a strict GFD for at least six months at the time of acute symptoms and tTG were trending down.