Open-Capsule Budesonide for Refractory Celiac Disease

Saurabh S. Mukewar, MBBS[1,4], Ayush Sharma, MBBS[1,4], Alberto Rubio-Tapia, MD[1], Tsung-Teh Wu, MD, PhD[2], Bana Jabri, MD[3] and Joseph A. Murray, MD[1]

OBJECTIVES: **Refractory celiac disease (RCD) is a rare condition often associated with poor prognosis. Various immunosuppressive medications (IMs) have been used with modest success. We describe outcomes in patients treated with open-capsule budesonide (OB), including those for whom IM treatment failed.**

METHODS: **We identified RCD patients treated with OB at Mayo Clinic, Rochester, Minnesota from 2003 to 2015. Demographic, serologic, and clinical variables were analyzed.**

RESULTS: **We identified 57 patients who received OB for suspected RCD. Based on clonal T-cell receptor gamma gene rearrangement or aberrant phenotype of intraepithelial lymphocytes (IELs), 13 patients (23%) were classified as having RCD-2 and 43 (75%) as RCD-1. In one patient (2%) TCR gene rearrangement status was unknown. Most patients were women (69%), mean (s.d.) age was 60.5 (3.5) years and body mass index was 28.4 (4.5) kg/m^2. The majority had diarrhea (72%), with median of 6 bowel movements per day (range, 4–25). IM treatment (azathioprine, systemic corticosteroids, or regular budesonide) had failed in nearly half. Twenty-four patients (42%) had anemia and 12 (21%) had hypoalbuminemia. All had Marsh 3 lesions on biopsy: 3a (19%), 3b (46%), and 3c (35%). After OB therapy, the majority had clinical (92%) and histologic (89%) improvement. Follow-up biopsy in 7 out of 13 patients with RCD-2 (53%) showed an absence of clonal TCR gamma gene rearrangement/aberrant IEL phenotype previously seen. On follow-up, 2 patients (4%) died of enteropathy-associated T-cell lymphoma.**

CONCLUSIONS: **Most patients with RCD show clinical and histopathologic improvement with OB therapy, including those with failure of IMs. OB is a promising therapeutic option for management of RCD.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol 2017; 112:959–967; doi:10.1038/ajg.2017.71; published online 21 March 2017

INTRODUCTION

Refractory celiac disease (RCD) is a severe but rare condition seen in <2% of patients with celiac disease (1–3). It is characterized by persistence or recurrence of malabsorptive symptoms and villous atrophy in patients with a previous diagnosis of celiac disease who have been on a gluten-free diet (GFD) for more than 6 months, and with no other causes of nonresponsive celiac disease or overt malignancy (4). Two types of RCD have been described—type 1 (RCD-1) is associated with normal CD3, CD4, and CD8 surface markers on lymphocytes, without clonal gene rearrangement of the gamma chain of the T-cell receptor (TCR), and type 2 (RCD-2) is associated with aberrant clonal intraepithelial lymphocytes (IELs) that lack surface expression of CD3, CD4, and CD8, and with TCR gamma gene rearrangement (5). Type 2 carries a worse prognosis because of a high risk of enteropathy-associated T-cell lymphoma (EATL) (5).

Treatment of RCD involves a strict GFD and immune suppression to reduce inflammation in the small bowel. Systemic glucocorticoids, budesonide, and immunosuppressive medications (IMs) have shown good clinical response with variable histologic response (6). In patients not responding to the above therapies, options are limited. In Europe, autologous stem cell transplant (ASCT) has been suggested for RCD-2 (ref. 7). At Mayo Clinic, we offer open-capsule budesonide (OB) for management of RCD,

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; [3]Department of Medicine, University of Chicago, Chicago, Illinois, USA; [4]Saurabh Mukewar and Ayush Sharma are first co-authors.
Correspondence: Joseph A. Murray, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA.
E-mail: murray.joseph@mayo.edu
Received 30 September 2016; accepted 10 February 2017

including for patients in whom traditional IMs have failed or even for previous treatment with enteric-coated (EC) budesonide. Our rationale for treating in this manner is that OB will likely ensure adequate drug delivery to the entire small bowel and not the distal ileum and colon, which is the target of treatment for EC budesonide. In the current series, we report our experience with use of OB for RCD during a 12-year period.

METHODS

Study design

This study was a retrospective case series of patients with RCD treated with OB. The Mayo Clinic Institutional Review Board approved the study. We searched the electronic health records at Mayo Clinic, Rochester, Minnesota, by using the terms "refractory celiac disease" or "nonresponsive celiac disease" to identify patients treated from January 1, 2003, to January 1, 2015. The charts retrieved were further searched with terms "budesonide" or "Entocort" to identify patients who received budesonide.

Inclusion and exclusion criteria

We included adult patients (>18 years) with a diagnosis of RCD who were treated with OB or a "Mayo compounded" capsule of budesonide, which is designed to release in the proximal upper gastrointestinal tract. Patients who were offered but never took OB and those treated only with EC budesonide or other IMs were excluded. Patients with symptoms secondary to gluten contamination or an uncertain diagnosis of RCD were also excluded. Patients receiving budesonide who had a non-RCD diagnosis such as inflammatory bowel disease, sprue like enteropathy associated with olmesartan, microscopic colitis, or autoimmune enteropathy were also (5,8,9) excluded.

OB treatment

Patients prescribed OB received oral budesonide 3 mg, 3 times a day. Directions for taking OB were as follows: (i) first daily capsule: open the capsule, empty contents into applesauce and stir, grind the medicine between the teeth, rinse and swallow with a glass of water; (ii) second daily capsule: open the capsule, empty contents into applesauce, stir, rinse and swallow with a glass of water; (iii) third daily capsule: swallow the whole capsule. The rationale for this protocol was to try to ensure adequate drug delivery to the entire small bowel including duodenum and jejunum. EC budesonide (Entocort) was designed for treatment of Crohn's disease. The Entocort (EC) capsule is designed to release drug in a pH- and time-dependent manner in order to target delivery in the distal small bowel and colon where most inflammation is seen in patients with Crohn's disease (10). The Entocort (EC) formulation of budesonide is available as 3 mg hard gelatin capsules containing the drug in 1 mm diameter round pellets. The active drug is contained in an insoluble ethylcellulose polymer, which provides time-dependent release of budesonide (11). It was theorized that opening the gelatin capsule and grinding the drug in the teeth will initiate release of budesonide from ethylcellulose polymer matrix, providing more immediate action in proximal small intestine. The EC budesonide capsule disintegrates and releases active drug in the distal small bowel and colon where most inflammation is seen in patients with Crohn's disease.

All patients while on OB treatment were instructed to avoid any drugs such as ketoconazole, oral contraceptive pills or foods such as grapefruit that are known to impair the cytochrome P3A4 function that is responsible for the high first pass inactivation of the active drug (11). The patients were advised to taper the OB using the following regimen once resolution of symptoms and at least substantial improvement in histology were achieved; 1 capsule three times a day (9 mg); 1 capsule two times a day (6 mg); 1 capsule once a day (3 mg); lastly 1 capsule every alternate day with dose adjustments occurring each 3 months.

Study variables

We extracted demographic and clinical variables for all patients. Age, sex, body mass index (BMI), family history of celiac disease, age at diagnosis of celiac disease, HLA-DQ typing, age at diagnosis of RCD, presentation of RCD (classic or atypical), type of RCD (RCD-1 or RCD-2), number of bowel movements per day at presentation of RCD, mode of nutrition (total parenteral nutrition, oral intake, or enteral feeding), albumin (g/dl), leukocyte count ($\times 10^3$/mcl), and hemoglobin (g/dl) were recorded. Previous treatment history was also noted (closed budesonide, azathioprine, or systemic glucocorticoids).

At presentation of RCD, serologic information was recorded: immunoglobulin A (IgA) tissue transglutaminase (TTG) antibodies, duodenal biopsy findings at presentation (Marsh (12)classification), TCR gamma gene rearrangement (clonal or polyclonal), and aberrant IEL phenotype. Other concomitant diagnoses at presentation (e.g., microscopic colitis, small intestinal bacterial overgrowth, lactose intolerance, pancreatic insufficiency) and medications used in addition to OB for treatment of RCD were also recorded (e.g., azathioprine, systemic glucocorticoids).

After treatment with OB, number of bowel movements/day, last duodenal biopsy findings (Marsh classification), adverse effects to OB and mortality were recorded. The patients who were continued on OB treatment, the last known date of taking OB was considered to be the duration of therapy at the point of follow up.

Definitions

RCD was defined as persistence or relapse of symptoms and intestinal damage in patients with previously confirmed celiac disease after strict adherence to a GFD diet for at least 6 months. RCD was diagnosed only after expert celiac dietician ensured there was no gluten contamination including in patients with low titers of tTG IgA. On the basis of TCR gene rearrangement and IEL phenotype, patients were classified as having RCD-1—persistent villous atrophy despite a strict GFD, associated with increased numbers of IELs, bearing a normal phenotype with surface CD3 and CD8 expression— or RCD-2—clonal expansion of abnormal IELs lacking surface markers CD3, CD8, and TCRs, and preserved expression of intracellular CD3 (6,13). Method for detecting TCR gene rearrangement: A PCR-based assay was performed on extracted DNA using primers that bind the gamma and beta

chain genes. Methods for immune-histochemical (IHC) staining studies: performed on paraffin sections of biopsy specimens using antibodies directed against the following antigens: CD3, CD8, TCR betaF1, and TCR gamma/delta.

Presentation of RCD was considered "classical" if it included diarrhea with or without associated symptoms such as weight loss, abdominal bloating, cramps, fatigue, dermatitis herpetiformis, and "atypical" if it did not include diarrhea but did include 1 or more of the other associated symptoms. RCD was classified as "primary" if patients had persistent symptoms after strict adherence to a GFD for 6 months and "secondary" if symptom relapse developed after initial response to a GFD. Anemia was defined as a hemoglobin value less than 13.5 g/dl for men and less than 12.5 g/dl for women. Leukocytosis was defined as a white blood cell count more than 11.0×10^9/l. Hypoalbuminemia was defined as serum albumin levels less than 3.5 g/dl.

Response to therapy

Clinical. Complete response was defined as regular bowel habits with weight gain and/or complete resolution of symptoms for "classical" presentation; for those with "atypical" presentation, complete response was defined as weight gain back to baseline with complete resolution of fatigue or abdominal symptoms and/or improvement in dermatitis herpetiformis rash. Partial response for "classical" presentation was improvement in bowel movements but not complete resolution of diarrhea or bowel movements back to baseline and/or persistent abdominal symptoms. For those with weight loss (atypical), partial response was defined as increase in weight but not back to baseline and/or decrease in abdominal symptoms but not complete resolution.

Histologic. Histologic response was defined on the basis of the Marsh-Oberhuber classification (2,12). Complete histologic response was defined as Modified Marsh grade 1 or 2 after OB therapy, and partial histologic response was defined as reversion of 1 stage or more in modified Marsh classification after treatment. We also confirmed the histologic response on the basis of the Corazza classification (14). Complete histologic response was defined as Corazza class A after OB therapy, and partial histologic response was defined as reversion of grade 2B to 2A after OB treatment (see **Supplementary Table S1** online).

Outcome

The primary outcome measure of this study was clinical and histologic response to OB. Secondary outcomes assessed were occurrence of EATL and death.

Statistical analysis

Continuous data were summarized using mean (standard deviation) or median (range) as appropriate. Baseline parameters were considered to be those determined at the time of starting OB treatment. The final results were compared using chi square *t* test for paired data. Statistical analysis was performed using JMP®, version 10 (SAS institute., Cary NC software). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Medical records of 228 patients with possible RCD were reviewed in detail; 171 were excluded because they did not fulfill the inclusion criteria (155 had other causes of nonresponsive celiac disease and 16 had RCD that did not receive OB; **Figure 1**). Fifty-seven patients with RCD receiving OB were included in the study.

Baseline characteristics

Most patients were women (69%), the mean (s.d.) age was 60.5 (3.5) years, and BMI was 28.4 (4.5) kg/m^2 (**Table 1**). The majority (72%) had classical symptoms of diarrhea, with a median of 6 bowel movements/day (range, 4–25). Sixteen (28%) did not have diarrhea, which represented atypical symptoms. Almost half (26, 46%) had a concomitant diagnosis: 12 (20%) microscopic colitis, 13 (23%) bacterial overgrowth, 2 (4%) lactose intolerance, and 2 (4%) pancreatic insufficiency. Total parenteral nutrition was required in 7 patients (12%) because of severe symptoms. Anemia was seen in 24 (42%), leukocytosis in 4 (7%) and hypoalbuminemia in 12 (21%) patients. Five (9%) were positive for TTG IgA antibody at low titers.

Four patients were on gluten free diet for <6 months; 3 patients for 5 months and 1 patient for 4 months. They were started on OB for presumed primary RCD as all of them were very sick, had severe disease requiring hospitalization and total parenteral nutrition. One of these patients was diagnosed as RCD 2 based on molecular studies.

On pretreatment duodenal biopsy, Marsh classification was 3b in 26 patients (46%), 3c in 20 (35%), and 3a in 11 (19%). Immunophenotyping was available in all except 1 patient (2%), whose RCD type was thus unknown. Of the other 56, 13 (23%) had clonal TCR gamma gene rearrangement or aberrant phenotype (RCD-2) and 43 (75%) did not (RCD-1). Flow cytometry analysis was available in 12 (21%) of patients and phenotype analysis was consistent with TCR gamma gene rearrangement in 7 patients.

Follow-up

Of the 57 patients, 3 were lost to follow-up and 3 had adverse effects to budesonide: 1 each had edema, fatigue, and nausea, and therefore therapy was discontinued. The median duration of follow up in 51 patients was 22 (range, 2–97) months. The duration of GFD was not a factor affecting the outcomes of OB treatment (see **Supplementary Table S2**). Among the 51 patients with follow-up data, 92% had clinical response (71% complete and 22% partial). Follow-up biopsy was obtained in 38 patients (74%). Histologic response was seen in 89% (63% complete and 26% partial). Of 13 RCD-2 patients with clonal TCR gamma gene rearrangement, 7 (54%) had an improvement in abnormal phenotype on follow-up biopsies. From these 7 patients, after OB treatment 6 had no clonal TCR detected by PCR, 1 had equivocal TCR and 5 had no aberrant phenotype by IHC on follow-up biopsies (**Table 2**). Median duration of difference between the pre- and post-OB treatment biopsies was 17 (range, 6 to 92) months. Even in patients with previous failure of IMs, high clinical (93%) and histologic response rates (91%) were observed. None of the

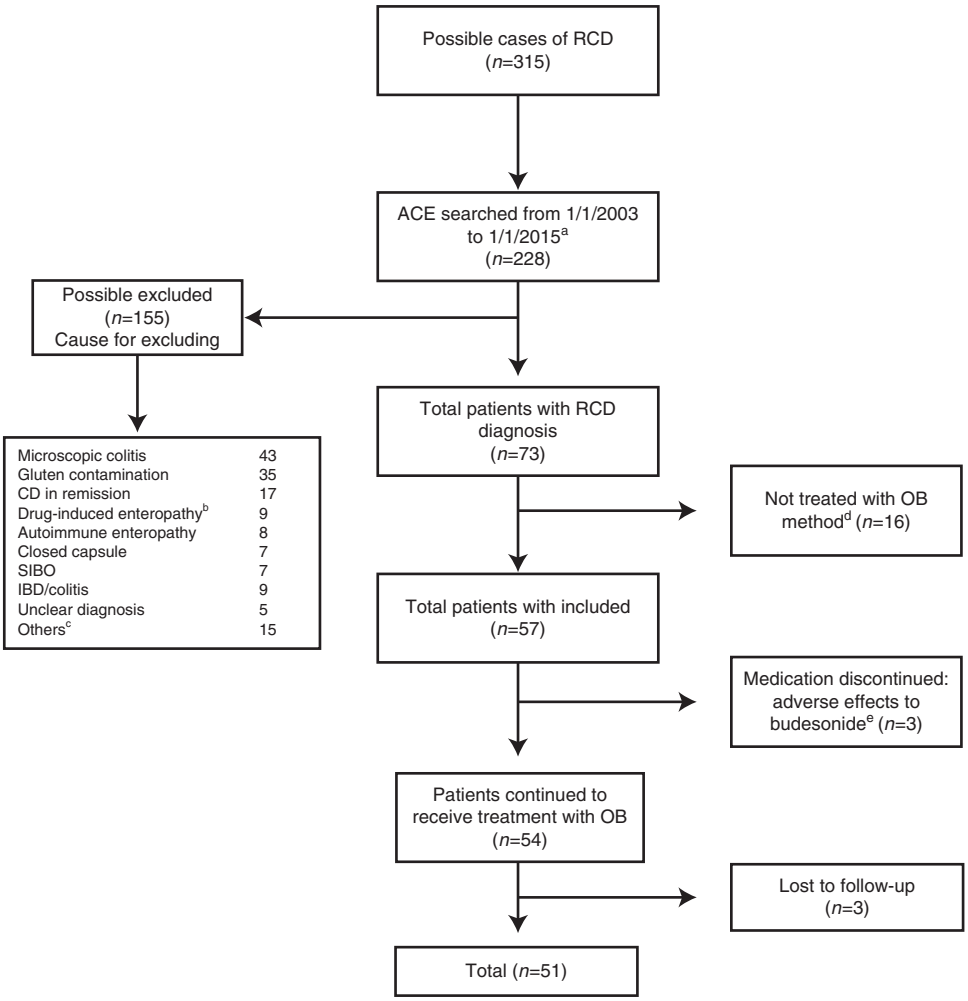

Figure 1. Flow diagram demonstrating study design and selection of patients. ACE, advanced cohort explorer; CD, celiac disease; IBD, inflammatory bowel disease; OB, open-capsule budesonide; RCD, refractory celiac disease; SIBO, small intestinal bacterial overgrowth. [a]ACE search terms "budesonide" and "Entocort." [b]Drugs included angiotensin-converting enzyme/angiotensin receptor blockers (*n*=6), nonsteroidal antiinflammatory drugs (*n*=1), and ipilimumab (*n*=1). [c]Others: common variable immunodeficiency (*n*=3), pancreatic insufficiency (*n*=1), immunoproliferative small intestinal disease (*n*=1), collagenous gastritis (*n*=1), autoimmune hepatitis (*n*=2), esophageal stricture (*n*=1), collagenous sprue (*n*=5), and T-cell proliferative disorder (*n*=1). [d]Other methods: closed capsule, Hu-Mik beta 1 trial, other immunomodulators, or budesonide in gel form. [e]Nausea (*n*=1), fatigue (*n*=1), and edema (*n*=1).

patients received cladribine or ASCT. One patient underwent surgery for duodenal adenocarcinoma.

Two patients had development of lymphoma. One patient with RCD-2 had lymphoma at presentation and died 6 weeks after starting treatment. The other patient had RCD-1, and lymphoma developed 56 weeks after starting treatment; the patient died 3 weeks after lymphoma diagnosis.

After excluding 6/57 patients with no follow up (*n*=3) and side effects to OB (*n*=3), and 1 patient who died from EATL after 4 weeks of treatment; the median duration of OB treatment was 15 (range, 2–118) months in 50 patients; 24 (48%) were tapered off OB and 26 (52%) were OB dependent—19 (73%) on low dose (3 mg or 6 mg/day) and 7 (27%) on full dose (9 mg/day).

For the patients tapered off OB (*n*=24) the median duration of treatment was 14 (range, 3–69) months; 18 (75%) were stable with no recurrence while 6 (25%) had relapse or mild persistent symptoms. For the patients who were continued on OB treatment (*n*=26) the median duration was 14 (range 5 to 118) months. Among OB dependent patients, 18 (69%) were stable with no recurrence of symptoms while 8 (31%) had mild persistent symptoms.

Type 1 vs. type 2 RCD

Patients with RCD-2 required TPN more often than RCD-1 (31 vs. 7%; *P*=0.02; **Table 1**). They also had more frequent prior history of treatment with IMs (77 vs. 42%; *P*=0.02). There were no significant differences in other factors between the 2 groups.

Most patients with RCD-1 and RCD-2 responded to therapy. A clinical response was noted in 92% of the RCD-1 group (68% complete and 24% partial) and in 92% of the RCD-2 group (77% complete and 15% partial; **Table 3**). A histologic response was observed in 89% of RCD-1 patients (67% complete and 22%

Table 1. Patient characteristics

Characteristic	Total (*N*=57)[a]	Type of RCD[b]		*P* value
		RCD-1 (*n*=43)	RCD-2 (*n*=13)	
Age (years)	60.5 (3.5)	60.4 (3.5)	74.2 (7.6)	0.37
Women	39 (69)	31 (72)	7 (54)	0.22
Body mass index (kg/m^2)	28.4 (4.5)	28.4 (4.5)	22.6 (0.2)	0.52
Family history of celiac disease[b]	15 (26)	13 (30)	1 (8)	—
Type of presentation	—	—	—	0.62
Classical[b]	41 (72)	30 (70)	10 (77)	—
No. of bowel movements/d	6 (4–25)	6 (4–25)	8 (5–15)	0.56
Weight loss[b]	32 (78)	22 (51)	9 (69)	0.24
Abdominal pain/bloating	19 (46)	11 (26)	8 (62)	0.12
Fatigue	8 (20)	6 (14)	2 (15)	1.0
Dermatitis herpetiformis	6 (15)	6 (14)	0	0.06
Atypical	16 (28)	13 (30)	3 (23)	—
Weight loss	9 (56)	7 (54)	2 (67)	0.68
Abdominal symptoms	14 (88)	11 (85)	3 (100)	—
Bloating	8 (50)	7 (54)	1 (33)	0.51
Pain	6 (38)	4 (31)	2 (67)	0.25
Fatigue	4 (25)	3 (23)	1 (33)	0.71
Dermatitis herpetiformis	4 (25)	4 (31)	0	0.16
TPN	7 (12)	3 (7)	4 (31)	0.02
Previous treatment[b]	29 (51)	18 (42)	10 (77)	0.02
Enteric-coated budesonide	16 (28)	12 (28)	3 (23)	—
Azathioprine	25 (44)	15 (35)	9 (69)	—
Systemic corticosteroids	8 (14)	6 (14)	2 (15)	—
Type of refractory state	—	—	—	0.17
Primary[b]	35 (61)	24 (56)	10 (77)	—
Secondary	22 (39)	19 (44)	3 (23)	—
Positive TTG	5 (9)	5 (12)	0	0.20
Anemia[b]	24 (42.1)	16 (37)	7 (54)	0.32
Leukocytosis	4 (7)	2 (5)	2 (15)	0.22
Hypoalbuminemia	12 (21)	7 (16)	5 (39)	0.12
No follow-up/adverse effects	6 (11)	6[c]	0	…

RCD, refractory celiac disease; TPN, total parenteral nutrition; TTG, tissue transglutaminase IgA antibody.
[a]Values are mean (s.d.), no. of patients (%), or median (range).
[b]Values are mean (s.d.) or no. of patients (%). One patient had no TCR gene analysis performed (indeterminate) and was not considered in baseline calculations.
[c]Three patients were lost to follow-up and 3 had adverse effects to budesonide (edema, fatigue, and nausea).

partial) and in 91% of RCD-2 patients (55% complete and 36% partial). There were no differences between the groups.

Previous immunomodulators

Half the patients (51%) had previous failed treatment with azathioprine, systemic corticosteroids, or regular budesonide. Those with prior IM therapy, more commonly had classical presentation, primary refractory state, requirement for TPN and RCD-2 diagnosis (see **Supplementary Table S3**). Most patients in both the groups responded to therapy. A clinical response was noted in 93% of prior treatment with IMs group (75% complete and 18% partial) and in 91% of no prior treatment with IMs group (65% complete and 26% partial; **Table 4**). A histologic response was observed in 91% of prior treatment with IMs group (56%

Table 2. Clonal status in patients with RCD type II before and after treatment with open method budesonide

	Pre OB-treatment		Post-OB treatment		Time between biopsies (months)
	TCR gene by PCR	Phenotype on IHC	TCR gene by PCR	Phenotype on IHC	
1	Clonal	Aberrant	No clonal	Normal	19
2	Clonal	Aberrant	NA	NA	—
3	Clonal	Aberrant	Clonal	NA	7
4	Clonal	Aberrant	Clonal	Aberrant	22
5	Clonal	Aberrant	Equivocal	Aberrant	92
6	Clonal	Normal	No clonal	Normal	13
7	Clonal	Aberrant	Clonal	Normal	46
8	Clonal	Aberrant	No clonal	Normal	7
9	Clonal	Normal	No clonal	Normal	24
10	Clonal	Aberrant	NA	NA	—
11	Clonal	Normal	No clonal	Normal	6
12	No clonal	Aberrant	No clonal	Normal	15
13	Clonal[a]	—	—	—	—

IHC, immunohisto-chemistry; NA, not applicable; OB, open method budesonide; PCR, polymerase chain reaction; TCR, T-cell receptor.
[a]EATL died within 5 weeks.
Biopsies revealed normal villous architecture, but no IHC or PCR was performed.

Table 3. Comparison of response between patients with RCD-1 and RCD-2

	Type of RCD[a]		
Response	RCD-1 (*N*=37)[b]	RCD-2 (*N*=13)	*P* value
Clinical	—	—	0.19
Complete	25 (68)	10 (77)	—
Partial	9 (24)	2 (15)	—
None	3 (8)	1 (8)	—
Histologic[c]	(*n*=27)	(*n*=11)	0.48
Complete	18 (67)	6 (55)	—
Partial	6 (22)	4 (36)	—
None	3 (11)	1 (9)	—

RCD, refractory celiac disease.
[a]Values are no. of patients (%).
[b]Excludes patients with adverse effects (*n*=3) and without follow-up (*n*=3).
[c]Excludes patients without follow-up biopsy and with missing data.

Table 4. Comparison of response between groups by prior treatment with immunosuppressors

	Prior treatment with immunomodulators[a]		
Response	Yes (*n*=28)[b]	No (*n*=23)[c]	*P* value
Clinical	—	—	0.19
Complete	21 (75)	15 (65)	—
Partial	5 (18)	6 (26)	—
None	2 (7)	2 (9)	—
Histologic[d]	(*n*=23)	(*n*=15)	0.48
Complete	13 (56)	11 (74)	—
Partial	8 (35)	2 (13)	—
None	2 (9)	2 (13)	—

RCD, refractory celiac disease.
[a]Values are mean (s.d.) or no. of patients (%).
[b]Adverse effect to budesonide: edema.
[c]Three patients were lost to follow-up and 2 had adverse effects to budesonide: fatigue and nausea.
[d]Excludes patients with without follow-up biopsy and with missing data.

complete and 35% partial) and in 87% no prior treatment with IMs group (74% complete and 13% partial). There was no difference between the groups.

DISCUSSION

This study demonstrates a positive effect of OB in patients with RCD. Nearly half had treatment failure with IMs, and, despite that prior failure of response to what might be considered potent therapy, most had clinical and histological improvement with topical budesonide alone. Interestingly, a complete histological response was observed in majority (24/38) cases who were revaluated after OB treatment. This was observed not only in RCD-1, but also in RCD-2, which is generally less responsive to therapy. OB was well tolerated, with very few adverse effects leading to discontinuation of therapy. On follow-up biopsies, absence of clonal

gene rearrangement and aberrant phenotype of IELs was noted in half of RCD-2 patients.

In this study, presentation of RCD was similar to that in some previous studies. Most patients were women with a mean age older than 50 years. Classic presentation with chronic diarrhea is seen in 80–90% of patients with RCD (15–17). Similarly, 73% of our patients had chronic diarrhea at presentation. The other 27% had other gastrointestinal tract symptoms such as abdominal pain, abdominal bloating, weight loss, or dermatitis herpetiformis. Similar to observations by Brar *et al.* (16) and Malamut *et al.* (17), almost half of our patients had primary presentation. Despite strict adherence to a GFD, nearly 8% had low titers of TTG IgA. This is postulated to occur secondary to ongoing inflammation and upregulation of TTG (15). In a study by Roshan *et al.* (15), almost 60% of cases had positive TTG antibodies. However, other studies have reported lower rates: ~20 –30% with positive TTG (13,16,17). One-third of patients in our study had total villous atrophy (Marsh 3c), similar to previous series (15–17).

Of interest, most patients in our study had RCD-1. This observation is similar to other series from the United States, with RCD-1 forming the major proportion of RCD cases. In contrast, studies from Europe have had a larger proportion of patients with RCD-2. Whether this is due to genetic/environmental factors or represents referral bias is unclear. RCD-2 cases appear to have a more severe presentation than RCD-1 (ref. 17). Higher rates of TPN requirement and lower hemoglobin and albumin levels were observed in RCD-2 compared with RCD-1 (ref. 17). Our observations were similar, with greater TPN requirement in RCD-2 patients.

Treatment of RCD involves immune suppression to reduce inflammation in the small bowel. Systemic glucocorticoids (prednisone) and budesonide in combination with immunomodulators such as azathioprine or anti-tumor necrosis factor agents have been used with variable success. When these therapies fail, ASCT or potentially toxic chemotherapy such as cladribine is recommended for RCD-2 (ref. 5). Clinical response rates generally have been reported in more than 90% of patients with RCD-1 (refs 18–20) but histologic improvement has not been consistently observed in these studies. In a series by Brar *et al.* (16), patients with RCD (mostly RCD-1) were treated with budesonide alone or in combination with systemic corticosteroids and azathioprine; no histologic response was seen in any of the 29 patients. A study by Malamut *et al.* (17) showed complete normalization of the mucosa in only 4 out of 10 patients with RCD-1 taking systemic corticosteroids. In contrast, some of the earlier, smaller studies from Europe had shown partial or complete normalization of villi in almost all patients with RCD-1 (refs 18,20). In the current study, close to half of RCD-1 patients (44%) had failure of conventional treatments. Despite inclusion of such patients with "refractory RCD," OB resulted in clinical as well as histological improvement in more than 90% of patients.

Patients with RCD-2 generally have lower clinical response rates (≈70–80%) compared with RCD-1 (refs 17,18). Histologic response in these cases is also much lower (0 to 33%; (refs 6,18,20)).

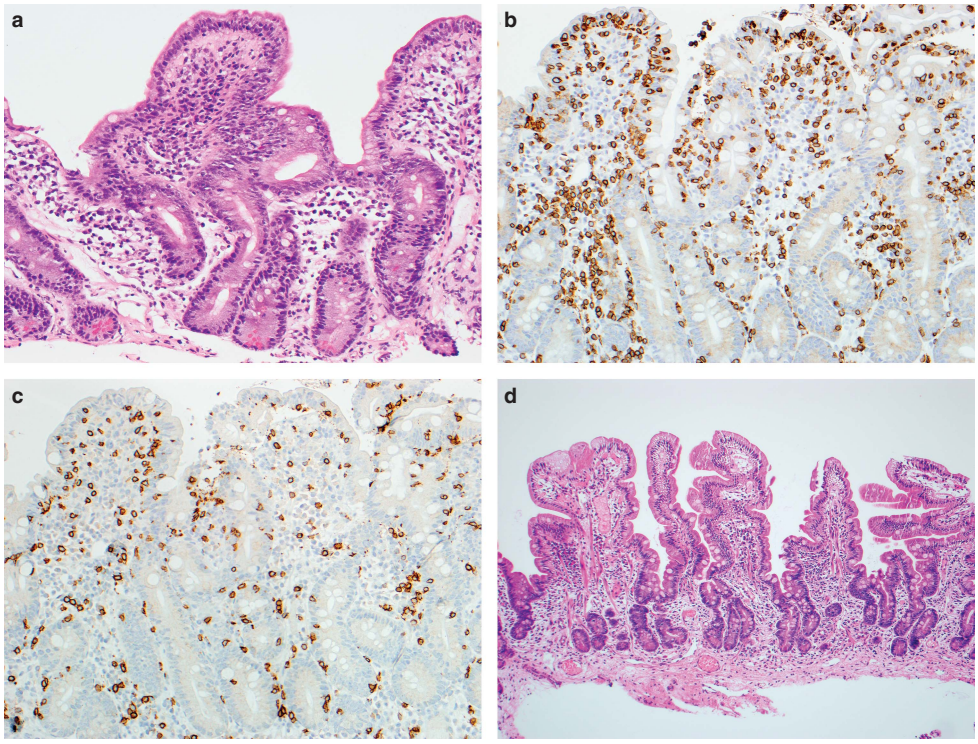

Figure 2. Intestinal histology before and after treatment. An example of RCD type II patient with duodenal biopsy showed partial villous atrophy with increased intraepithelial lymphocytes (IELs) (**a**) before treatment with open capsule budesonide. The intraepithelial lymphocytes were positive for g CD3 (**b**) but negative for CD8 (**c**) by immunostain before treatment with open capsule budesonide. The duodenal biopsy showed normal villous architecture with no increased I intraepithelial lymphocytes after treatment with open capsule budesonide (**d**).

In one of the earlier studies by Cellier *et al.* (21), 8 out of 12 RCD-2 patients had clinical response but none had a change in histology. In another study, only 2 out of 8 RCD-2 patients had slight improvement in histology (20). In the study by Malamut *et al.* (17), 10 out of 30 patients had histologic improvement: 7 partial and 3 complete, with systemic corticosteroids. None of these series showed absence of TCR gene rearrangement in follow-up biopsies. Consequently, EATL has developed in 40–70% of patients with RCD-2 treated with conventional IMs (6,13,15,22). In contrast, the current study shows much higher rates of clinical and histological improvement (>90%) in RCD-2 patients receiving OB (**Figure 2**). Most had failure of previous immune modulator therapies. Importantly, the absence of aberrant phenotype of IELs/TCR gene rearrangement was seen in 7/13 patients (54%). None of these 7 patients had EATL. Of the other 6 patients with no change in IEL phenotype or TCR gene rearrangement, 1 died of EATL. These results should be interpreted cautiously due to small sample size and heterogeneous follow-up.

RCD involves the mucosal layer of the small intestine. When selecting therapy, local delivery of drug with minimal adverse effects is desirable. OB has potent anti-inflammatory effects and acts via the enteral route on this mucosal surface. Systemic immunomodulators may not achieve this level of immune suppression at these targeted areas in the small intestine. In our clinical experience, we have also used OB for other inflammatory small intestinal conditions, such as autoimmune enteropathy and collagenous sprue, with high success rates (9,23). Importantly, OB does not have systemic toxicity, and none of the patients in current series had any systemic adverse effects or contracted opportunistic infections. Although one patient after OB treatment for 9 years developed some skin bruising requiring dose deescalation. A systematic evaluation of adrenal suppression was not undertaken. However none of these patients developed appreciable cushingoid side effects while on treatment. Even so, it is possible that the systemic bioavailability of budesonide may vary based on mucosal integrity as was suggested to occur early in treatment of Crohn's disease (11). The absence of TCR gene rearrangement in a significant proportion of our cases is likely due to such potent immune suppression locally in the small intestine.

This study has important implications. Despite including a large proportion of cases that failed to respond to conventional therapy, we observed more than 90% clinical and histological improvement in both RCD-1 and RCD-2 patients treated with OB. Most patients tolerated this well without any significant adverse effects. None of these patients required ASCT. Thus, in view of this open-label experience, OB may be considered as an alternative for systemic steroids and should undergo robust testing as a therapy for RCD patients with or without failure of conventional immune suppression therapy. Improvement in aberrant phenotype or absence of TCR gene rearrangement was observed in more than half the patients treated with OB. Rates of EATL in the current study were lower than in other studies, possibly because of the large number of RCD-1 cases in our study. In our earlier experience, we demonstrated a case of EATL developing in a patient treated with cladribine and absence of TCR gene rearrangement on follow-up biopsy (13). However, we suspect that the overall risk of EATL is decreased if there is absence of TCR gene rearrangement on follow-up biopsies, as evidenced in the current study. Thus, OB may have the potential to reduce the risk of EATL in RCD-2 patients although longer clinical follow-up is needed.

Strengths of this study include a large series of patients with RCD. Analysis of TCR gene rearrangement and biopsies were performed in most of our patients. We have described a novel and a safe method for treatment of a severe illness, with the potential to avoid toxic therapy and the future development of malignancy. Limitations include the retrospective nature of the study, open-label experience, lack of a comparison group, limited follow up period, a relatively smaller proportion of compromised and RCD-2 patients and only small percentage of patients had data available on flow cytometry.

In conclusion, OB is effective in inducing and maintaining clinical as well as histological response in RCD, including in those who have had failure of IM treatment. The absence of TCR gene rearrangement on follow-up biopsies can be seen in a high proportion of RCD-2 patients, with potential to prevent EATL. Rigorous prospective studies are needed to validate these findings.

ACKNOWLEDGMENTS

We acknowledge the revision and edits provided by scientific publication services at Mayo Clinic, Rochester, MN, USA.

CONFLICT OF INTEREST

Guarantor of the article: Joseph A. Murray, MD.

Specific author contributions: Study concept and design: Saurabh Mukewar, Ayush Sharma, and Joseph Murray; acquisition of data: Ayush Sharma and Saurabh Mukewar; analysis and interpretation of data: Ayush Sharma and Saurabh Mukewar; drafting of manuscript: all authors; critical revision: all the authors.

Financial support: None.

Potential competing interest: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Refractory celiac disease (RCD) treatment involves strict gluten-free diet (GFD) and immunosuppressive therapy.
- ✓ Immunosuppressive medications have shown good clinical response but variable histological response.
- ✓ Type II RCD has a higher risk of lymphoma and failure of immunosuppressive therapy requires treatment with autologous stem cell transplant or chemotherapy.

WHAT IS NEW HERE

- ✓ Open capsule budesonide (OB) treatment in RCD patients resulted in excellent clinical and histological response in majority of the patients.
- ✓ Response was also seen in patients who previously failed treatment with immunosuppressive medications (IMs).
- ✓ There was also absence of clonal T-cell receptor (TCR) or aberrant phenotype seen in some RCD-2 patients.

REFERENCES

1. Jafri MR, Nordstrom CW, Murray JA *et al.* Long-term fracture risk in patients with celiac disease: a population-based study in Olmsted County, Minnesota. Dig Dis Sci 2008;53:964–71.
2. Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother 2000;54:368–72.
3. West J. Celiac disease and its complications: a time traveller's perspective. Gastroenterology 2009;136:32–4.
4. Biagi F, Bianchi PI, Trotta L *et al.* Anti-goblet cell antibodies for the diagnosis of autoimmune enteropathy? Am J Gastroenterol 2009;104:3112.
5. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut 2010;59:547–57.
6. Malamut G, Murray JA, Cellier C. Refractory celiac disease. Gastrointest Endosc Clin N Am 2012;22:759–72.
7. Al-toma A, Visser OJ, van Roessel HM *et al.* Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. Blood 2007;109:2243–9.
8. DeGaetani M, Tennyson CA, Lebwohl B *et al.* Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol 2013;108:647–53.
9. Akram S, Murray JA, Pardi DS *et al.* Adult autoimmune enteropathy: Mayo Clinic Rochester experience. Clin Gastroenterol Hepatol 2007;5:1282–90; quiz 1245.
10. Entocort EC (budesonide) Capsules [package insert] Wilmington, DA, Astra Zeneca. Accessed on March 3rd, 2017, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021324s009lbl.pdf. 2012.
11. Edsbäcker S, Bengtsson B, Larsson P *et al.* A pharmacoscintigraphic evaluation of oral budesonide given as controlled-release (Entocort) capsules. Aliment Pharmacol Ther 2003;17:525–36.
12. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–54.
13. Rubio-Tapia A, Kelly DG, Lahr BD *et al.* Clinical staging and survival in refractory celiac disease: a single center experience. Gastroenterology 2009;136:99–107; quiz 352-3.
14. Corazza G, Villanacci V. Coeliac disease. J Clin Pathol 2005;58:573–4.
15. Roshan B, Leffler DA, Jamma S *et al.* The incidence and clinical spectrum of refractory celiac disease in a north american referral center. Am J Gastroenterol 2011;106:923–8.
16. Brar P, Lee S, Lewis S *et al.* Budesonide in the treatment of refractory celiac disease. Am J Gastroenterol 2007;102:2265–9.
17. Malamut G, Afchain P, Verkarre V *et al.* Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. Gastroenterology 2009;136:81–90.
18. Cellier C, Delabesse E, Helmer C *et al.* Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. The Lancet 2000;356:203–8.
19. Daum S, Ipczynski R, Schumann M *et al.* High rates of complications and substantial mortality in both types of refractory sprue. Eur J Gastroenterol Hepatol 2009;21:66–70.
20. Harris PA, Taylor R, Thielke R *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
21. Cellier C, Cerf-Bensussan N. Treatment of clonal refractory celiac disease or cryptic intraepithelial lymphoma: a long road from bench to bedside. Clin Gastroenterol Hepatol 2006;4:1320–1.
22. Al-Toma A, Verbeek WH, Hadithi M *et al.* Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut 2007;56:1373–8.
23. Murray JA, Rubio-Tapia A. Diarrhoea due to small bowel diseases. Best Pract Res Clin Gastroenterol 2012;26:581–600.