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Oral Viscous Budesonide: A Potential New Therapy for Eosinophilic Esophagitis in Children

Seema S. Aceves, M.D., Ph.D.,[1,4] John F. Bastian, M.D.,[1,4] Robert O. Newbury, M.D.,[2] and Ranjan Dohil, M.D.[3,4]

Divisions of [1]Allergy and Immunology, [2]Pathology, and [3]Gastroenterology, Children's Hospital, San Diego, La Jolla, California; and [4]Department of Pediatrics, University of California, San Diego, La Jolla, California

BACKGROUND: Eosinophilic esophagitis (EE) is a disorder characterized typically by pan-esophageal eosinophilia. We evaluate a palatable, long-acting topical corticosteroid preparation for the treatment of EE.

STUDY DESIGN: This is a retrospective analysis of symptoms, endoscopic and histologic findings, efficacy, and safety of treatment in children with EE receiving oral viscous budesonide. Response to therapy was determined histologically by the number of eos/hpf. Patients were classified by histology into *responders* (0–7 eos/hpf), *partial responders* (8–23 eos/hpf), and *nonresponders* ($\geq$24 eos/hpf). A symptom score (max. 14) and an EE endoscopy score (max. 8) were used to compare data.

RESULTS: In 20 children (mean age 5.5 yr, median age 4.1 yr) the mean highest eosinophil count was 87 eos/hpf (range 30–170) before and 7 eos/hpf (range 0–50, $P < 0.0001$) after therapy. There were 16 (80%) *responders*, 1 *partial responder*, and 3 *nonresponders*. Commonest pretreatment symptoms were nausea, vomiting, pain, and heartburn. The mean symptom score fell from 4.4 to 0.8 ($P < 0.0001$) and the mean endoscopy score from 3.6 to 0.8 ($P < 0.0001$). No significant adverse events were reported. Morning cortisol levels were within normal limits.

CONCLUSIONS: Topical viscous budesonide is a safe and effective therapy for EE in young children.

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INTRODUCTION

Eosinophilic esophagitis (EE) is a disease most likely due to an immunologic response to ingested and inhaled allergens (1–5). Eosinophilic esophagitis often has characteristic endoscopic features, but is diagnosed when $\geq$20 to $\geq$24 eosinophils/high power field (eos/hpf) are found in esophageal mucosal biopsies (6–12). Although EE is becoming more frequently diagnosed (7, 8, 13–16) many aspects of the disease remain unclear including its etiology, natural history, and optimal therapy. Presenting symptoms of EE often mimic those of gastroesophageal reflux disease (GERD) and include vomiting, dysphagia, pain, and food impaction (8, 14, 17–20). However, because the treatment of EE and GERD differ, it is important to distinguish between them where possible by endoscopic and histologic means. Untreated EE may be associated with esophageal narrowing, with strictures being reported at presentation in 30% of adults and in 10% of children (14, 18, 20, 21).

Therapeutic options for EE include specific food elimination (22, 23), elimination diet with an elemental formula (2, 24), topical and systemic corticosteroids (25–30). Identifying true inciting food allergens can be difficult and elemental formulas are often unpalatable, thereby making dietary interventions complicated (1, 22). Systemic corticosteroids and swallowed topical steroids, such as fluticasone propionate (Flovent™) administered through metered-dose inhaler (MDI), have been shown to induce and maintain low esophageal eosinophil levels (25–30). However, aerosolized corticosteroids may be difficult for young children to ingest, which are often bitter to taste and require twice daily administration. We recently reported the successful treatment of EE using an oral viscous suspension of budesonide (Pulmicort™) in 2 patients who were unable to utilize fluticasone propionate for developmental reasons (28).

In this report we have expanded our trial and described the efficacy and safety of once daily oral viscous budesonide (OVB) in inducing and maintaining remission of disease activity in children with EE.

METHODS

This retrospective review was approved by Children's Hospital, San Diego (CHSD) and University of California at San Diego (UCSD), Human Research Protection Program. Patients were referred from CHSD subspecialty clinics and other institutions to the EE clinic. Treatment with proton pump inhibitors (PPI), elimination diet based upon skin or blood allergy testing, elemental diet, or topical fluticasone propionate were all evaluated. Patients who failed in these

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therapies, refused elimination diet, or were unable to utilize fluticasone propionate MDI but continued to have ≥24 eos/hpf on esophageal biopsy were offered OVB. Patients were defined as having food or aeroallergen sensitization if RAST and/or skin prick testing were positive. No changes were made to longstanding therapy used for treating chronic conditions such as asthma or eczema and none of the children received concurrent immune-modulatory therapy. Blood samples for morning cortisol measurements were taken between 8:00 AM and 9:00 AM and were processed by Mayo Medical Laboratories by automated chemiluminescent immuno-enzymatic assay (BeckmanCoulter, Fullerton, CA).

Upper Gastrointestinal Endoscopy and Biopsy

Endoscopy was performed using the Olympus P160 endoscope (Olympus, Mellville, NY) (by RD) in symptomatic patients. Pan-esophageal, gastric (antrum and body), and duodenal biopsies were taken. Eosinophilic esophagitis was diagnosed when ≥24 eos/hpf were found in at least one of the esophageal sites biopsied. Two mucosal biopsies were taken from each of the proximal esophagus (3 cm below the crycopharyngeus muscle), distal esophagus (3 cm above the gastroesophageal junction [GEJ]), and mid-esophagus (midpoint between the crycopharyngeus muscle and the GEJ). Biopsies were processed routinely and evaluated by a pediatric pathologist (RN). The highest number of eosinophils per ×400 high power field was counted (Fig. 1A). Basal zone hyperplasia (BZH) was reported when basal zone cells extended towards the luminal surface of the epithelium (>25% of epithelial thickness).

Follow-up endoscopy with biopsies was performed after 3–4 months of OVB treatment in all subjects. Counting the highest number of eos/hpf within biopsies determined the response to therapy and patients were categorized into *responders* (0–7 eos/hpf), *partial responders* (8–23 eos/hpf), and *nonresponders* (≥24 eos/hpf).

An EE endoscopy score was devised to compare findings before and after treatment. It was calculated from procedure reports and photographs. Four categories were used: (1) pallor and diminished vascular markings, (2) furrowing with "thickened" mucosa, (3) white mucosal plaques, (4) concentric rings or strictures. For each category, one point was allocated if 1 or 2 esophageal sites were involved, and two points for pan-esophageal involvement. The maximum score was 8.

Treatment

Patients received OVB 1–2 mg daily and were instructed not to ingest any solid or liquid food for 30 minutes after its administration. Children under the age of 10 yr received OVB 1 mg daily and those who were 10 yr or over received 2 mg/day. Viscous budesonide was made by mixing each 0.5 mg Pulmicort Respule™ with 5 g (5 packets) of sucralose (Splenda™) to create a volume of 8–12 mL. A Pulmicort Respule™ is liquid budesonide intended for nebulized administration (0.5 mg budesonide/2 mL). No dietary changes were made before OVB therapy in patients already on dietary restrictions. All patients received concurrent acid-suppression therapy. Compliance to therapy was determined by direct questioning during outpatient follow-up and immediately before endoscopy.

Symptoms

A modified symptom score based on children with acid-peptic disease is used routinely in the EE clinic (31). The symptom categories included (1) heartburn or regurgitation, (2) abdominal pain or unexplained irritability in children, (3) nausea or vomiting, (4) anorexia or early satiety, (5) dysphagia or odynophagia, (6) nocturnal wakening with symptoms, (7) gastrointestinal bleeding (previous 4 months). Each category scored 0–2 points with a maximum of 14 points. Zero points were awarded if the symptom was absent; 1 point if the symptom was mild, did not interfere with daily activities; 2 points if the symptoms were severe enough to interrupt daily activities. Previous GI bleeding was considered mild (1 point) if there was no associated hemodynamic compromise or anemia, and severe (2 points) if bleeds were multiple, caused anemia, or required blood transfusion.

Statistical Analysis

All statistical analysis was carried out using the NCSS Statistical Software package (NCSS Statistical Software, Kaysville, UT). Two-tailed P values were calculated using paired t-tests to compare the means of patient values for eos/hpf, EE endoscopy scores, and symptom scores before and after budesonide therapy. Two-tailed unpaired t-tests were utilized in order to compare variables grouped by *responders versus nonresponders*. Spearman's correlation coefficients were generated using GraphPad Prism software (Graph-Pad Software, Inc., San Diego, CA). Results with P values <0.05 were considered statistically significant. Both mean and median statistics were generated, both were equivalent, and mean statistics are presented.

RESULTS

Subjects

Chart reviews were undertaken on 20 children with EE who were treated with OVB. The median age was 4.1 yr and the mean age was 5.5 yr (range 1.7–17.6 yr). Fifteen were white, 2 Hispanic, 2 Asian, and 1 African American. Three children had developmental delay (1 cerebral palsy, 1 autism, and 1 Rett's syndrome), and one had mild IgG deficiency (321 mg/dL, reference range 423–1,090 mg/dL). Fourteen children had asthma, eczema, and/or allergic rhinitis, 16 had sensitization to foods based on positive skin and/or RAST testing (Table 1). Prior to OVB, 6 children failed monotherapy with either elimination diet (3) or fluticasone propionate (3), 5 children failed fluticasone either with (2) or without PPI (3) therapy, and 5 children failed PPI monotherapy. Four children did not receive any therapy prior to treatment with OVB. Three of the children on elimination diet received between 50% and 80% of their caloric intake through elemental formula. All treated children underwent repeat endoscopy while

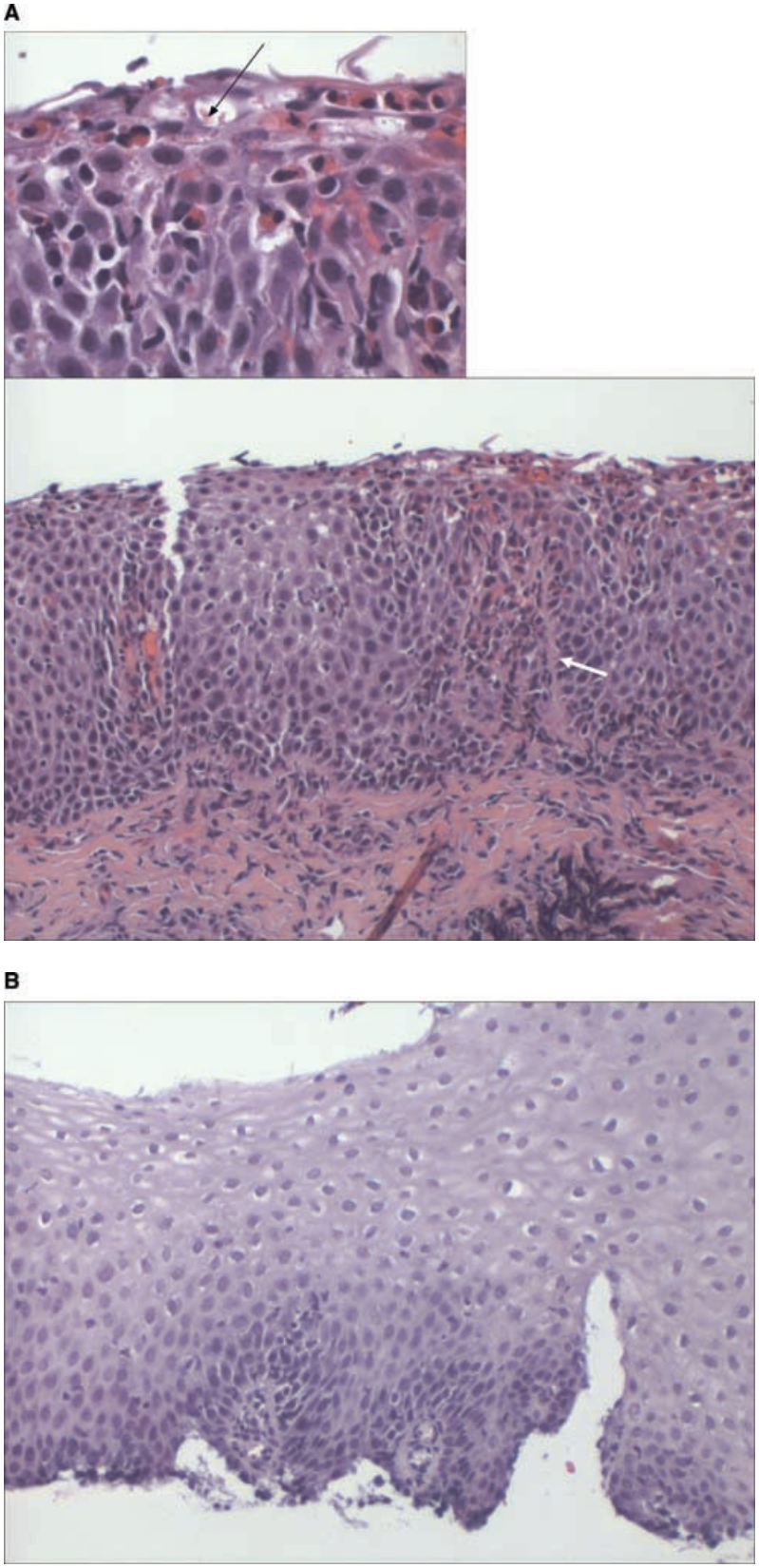

Figure 1. (*A*) Pretreatment distal esophageal biopsy showing marked basal zone hyperplasia (white arrow), numerous intraepithelial eosinophils (black arrow) with a few degranulated eosinophils, intercellular edema, and fibrosis of the lamina propria (hematoxylin & eosin, original magnification × 125; inset × 500). Basal zone hyperplasia is reported when basal zone cells extend towards the luminal surface of the epithelium (>25% of epithelial thickness). (*B*) Posttreatment distal esophageal biopsy showing normalization. Note absence of eosinophils and intercellular edema (hematoxylin & eosin, original magnification × 125, inset × 500).

Table 1. Patient Characteristics Pre- and Post-Viscous Budesonide Therapy. Patient Response Was Determined by Counting the Highest Eosinophil Count/hpf After Viscous Budesonide and Categorized into *Responders (*0–7 eos/hpf), *Partial Responders* (8–23 eos/hpf), and *Nonresponders* (≥24 eos/hpf)

Patients	Age Months	Response Category	Sex	Weight Change Per Month	Specific IgE*	Prior† Therapy (Months)	PPI† Before Budesonide	Budesonide Dose in mg (Months)	Highest eos count/ hpf Pre- /Post-Budesonide			Basal Zone Hyperplasia (Site‡)		Endos-copy Score		Symptom Score	
									Site‡	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	42	Responder	M	−0.1	F, A	ELIM (4)	No	1 mg (4)	M	70	1	Yes (P, M, D)	Yes (P, M)	6	1	3	2
2	33	Responder	M	0.15	None		Yes	1 mg (3)	D	30	7	Yes (D)	Yes (D)	1	0	7	3
3	71	Responder	M	0.73	F, A		Yes	1 mg (3)	D	74	0	Yes (P, D)	No	2	0	5	0
4	109	Responder	M	0.85	None	FLU (3)	Yes	1 mg (4)	M	100	2	Yes (M, D)	No	4	2	4	0
5	41	Responder	M	−0.07	F, A	ELIM (2)	Yes	1 mg (3)	D	50	0	Yes (M, D)	No	2	1	8	3
6	66		M		F, A	FLU (3)		1 mg (3)	P	60	50			6	1	4	3
		Responder	M	0.5	F, A		Yes	2 mg (3)	P	50	0	Yes (M)	No	1	0	3	2
7	88		M		F, A	FLU (12)	Yes	1 mg (3)	D	50	80			4	4	0	0
		Responder		0.375			Yes	2 mg (3)	D	80	1	Yes (P, M, D)	No	4	0	0	0
8	90	Responder	F	0.65	None		No	1 mg (4)	P	170	0	Yes (P, D)	No	6	1	9	0
9	41	Responder	M	0.18	A		Yes	1 mg (4)	P, D	70	0, 0	Yes (P, M, D)	No	2	0	3	0
10	20	Responder	M	0.03	F		Yes	1 mg (4)	D	80	0	Yes (P, M, D)	No	4	0	3	0
11	201	Responder	F	0.1	A		No	2 mg (4)	D	130	0	Yes (P, M, D)	No	6	0	5	1
12	34	Responder	M	−0.15	None		No	1 mg (3)	D	100	0	Yes (P, M, D)	No	5	0	3	0
13	51	Responder	F	0.08	F	ELIM (5)	No	1 mg (6)	D	120	0	Yes (D)	No	2	0	0	0
14	48	Responder	M	1.5	F	ELIM (5)	No	1 mg (3)	D, M, P	30	0	Yes (P, M, D)	No	4	0	3	0
15	31	Responder	M	0.2	F	ELIM (3)	Yes	1 mg (4)	D	100	5	Yes (P, D)	No	2	0	7	0
16	121	Responder	M	0.13	F, A		Yes	2 mg (3)	M	90	3	Yes (P, M, D)	Yes (P, M, D)	4	2	4	1
17	36	Partial responder	M	0.46	F, A	FLU (12)	No	0.5 mg (3)	D	100	16	Yes (M, D)	No	6	1	6	2
18	32	Nonresponder	M	0.83	F		No	1 mg (3)	D	100	50	Yes (M, D)	Yes (P, D)	2	3	3	1
19	68	Nonresponder	F	0.15	F	ELIM (2)	Yes	1 mg (4)	D	100	28	Yes (P, M, D)	Yes (P, M, D)	4	0	2	0
20	93	Nonresponder	M	0.15	F, A	FLU	No	1 mg (4)	D	100	25	Yes (P, M, D)	Yes (P, M, D) (P, M, D)	5	2	8	0

Patient 6 and 7 failed treatment with 1 mg viscous budesonide, but responded to an increased dose.
Patient 11 was started on 2 mg viscous budesonide because of her age and size.
Patient 16 had dose increased from 1 mg to 2 mg viscous budesonide after one month because symptoms persisted on lower dose.
*Sensitization to food (F) or aeroallergens (A) as determined by RAST or skin-prick testing.
†Before starting OVB subjects failed therapy with elimination diet (ELIM), topical fluticasone propionate, and/or proton pump inhibitors (PPI).
‡Site of esophageal involvement is divided into distal (D), mid (M), and proximal (P).
The highest eosinophil count/hpf, presence of basal zone hyperplasia, endoscopy, and symptom scores are given pre- and post-viscous budesonide therapy.
Maximum endoscopy score is 8 and maximum symptom score is 14.

Table 2. Esophageal Eosinophil Count Pre- and Post-Viscous Budesonide for Different Patient Response Categories. Mean Values and Standard Error of the Mean (SEM) in Parentheses are Provided for the Highest Esophageal Eosinophil Counts (eos/hpf) Measured Within the Whole Esophagus

	Esophagus eos/hpf Mean (SEM)	
Response Category	Pre	Post
Responders N = 16	84 (9)	1.4** (0.6)
Partial responder N = 1	100	20
Nonresponders N = 3	100 (0)	34* (8)

*$P < 0.05$; **$P < 0.001$; categories without asterisks do not reach statistical significance.

on therapy and had >24 eos/hpf on esophageal biopsy before starting OVB therapy. Five of the 9 children who did not receive elimination diet or fluticasone propionate before starting OVB did receive PPI therapy (Table 1).

Mean morning cortisol level measured in 18 patients was 9.5 μg/dL (patient range 6–17 μg/dL, normal range 2–17 μg/dL). Seventeen children gained weight during treatment at a mean rate of 0.42 kg per month. No adverse effects attributable to OVB were noted except for one child with low IgG who developed esophageal candida.

Treatment

Patients received OVB for 3 to 4 months before repeat endoscopy. Initially seventeen patients received OVB 1 mg/day, 2 patients received 2 mg/day, and 1 patent unintentionally received 0.5 mg/day. Two patients failed treatment with OVB 1 mg daily and their dose was increased to 2 mg/day (Table 1).

HISTOLOGY. Before treatment the mean highest eosinophil count for all patients, for all sites, was 87 eos/hpf (95% CI 72–103, with a median of 95, range 30–100), with a mean of 80 eos/hpf (95% CI 66–94) in the distal, 53 eos/hpf (95% CI 37–68) in the mid-, and 43 eos/hpf (95% CI 24–61) in the proximal esophagus. The highest eosinophil count was found in distal esophageal biopsies in 14, mid-esophageal in 3 patients, and proximal esophageal biopsies in 3 other patients. Ten patients (50%) had pan-esophageal BZH. The gastric and duodenal biopsies were normal. Following treatment, the final mean highest esophageal eosinophil count for all patients was 7 eos/hpf (95% CI 1–13, $P < 0.0001$, with a median of 0.5 eos/hpf and range of 0–50). This mean level was calculated using esophageal eosinophil counts obtained after treatment with OVB 2 mg/day in 2 patients (nos. 6 and 7, Table 1) who had failed OVB 1 mg/day. All patients had a decreased eosinophil count with mean levels of 9 (95% CI 9–14) in distal, 5 (95% CI 1–9) in mid-, and 2 (95% CI 1–5) eos/hpf in the proximal esophagus. Sixteen patients were histologic responders, 1 *partial responder*, and 3 patients were *nonresponders* (Table 1 and 2). There was no difference in age, height, dose, or duration of therapy between the 16 histologic *responders* and the 4 *partial* or *nonresponders*. One *partial responder* had received OVB 0.5 mg/day; his highest count fell from 100 to 16 eos/hpf. The 3 *nonresponders* still demonstrated 50–75% improvement in their highest counts with treatment (Table 1 and 2). Despite incomplete histologic resolution, all *nonresponders* had improvement in their symptom scores (Table 4) and 2 of 3 patients had improvement in their endoscopy scores for pallor, furrowing, and plaques (Table 1 and 3). Therefore, histologic nonresponse did not always correlate with symptomatic or endoscopic nonresponse. All *nonresponders* received OVB 1 mg/day. Of the 5 patients who were nonresponders to fluticasone propionate, 3 were histologic *responders*, 1 was a *partial responder,* and 1 patient was a *nonresponder* to OVB therapy; the nonresponder still had a >70% drop in highest eosinophil count during treatment (Table 1).

BZH resolved completely in 6 of the 10 children with pan-esophageal findings. These patients were all histologic *responders* (Table 1).

UPPER GASTROINTESTINAL ENDOSCOPY. Before treatment, the mean EE endoscopy score for all patients was 3.6 (range 1–6). The commonest findings were pallor (90%), linear furrowing (80%), and white plaques (50%). Following treatment the mean EE endoscopy score was 0.8 (range 0–5). The EE endoscopy score fell to 0 in 12 children and improved in 19 children. Eleven children with complete normalization were histologic *responders* and 1 was a *nonresponder* (>70% fall in eosinophil count). One child with an EE endoscopy scores that did not improve was a histologic *nonresponder* (Tables 1–3 and Fig. 2).

Table 3. Eosinophilic Esophagitis Endoscopy Scores, Pre- and Post-Viscous Budesonide Therapy, for Different Response Categories. Maximum Total Score Is 8 and Maximum for Each Category Is 2. Standard Error of Mean Shown in Paratheses

	Total Score Mean (SEM)		Pallor Mean (SEM)		Furrows Mean (SEM)		Plaques Mean (SEM)		Esophageal Rings	
Response Category	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Responders N = 16	3.4 (0.4)	0.4** (0.2)	1.4 (0.2)	0.3** (0.2)	1.3 (0.2)	0.2** (0.1)	0.8 (0.2)	0 *(0)	None	None
Partial responder N = 1	6	1	2	0	2	1	2	0	None	None
Nonresponders N = 3	3.7 (0.9)	1.7 (0.9)	1.7 (0.3)	0.7* (0.3)	1 (0.6)	0.3 (0.3)	1 (0.6)	0.3 (0.3)	None	None

* $P < 0.05$; ** $P < 0.001$; categories without asterisks do not reach statistical significance.

SYMPTOM SCORE. Before treatment the mean symptom score for all patients was 4.4 and following treatment fell to 0.8 ($P < 0.0001$). Eighteen children had an improved symptom score and 11 had a score of 0. Eight of these 11 patients were histologic *responders* with complete endoscopic resolution. Two children had symptom scores of 0 before and after OVB therapy. Although these 2 children had symptom resolution on elimination diet or fluticasone, histologic resolution did not occur until after treatment with OVB. The 5 patients who took only PPI therapy prior to budesonide did not have a significant improvement of symptoms on acid-suppression therapy alone (Tables 1, 2, 4).

There was a statistically significant correlation between the number of eosinophils and the endoscopy and symptom scores (Spearman r of 0.64 and 0.84 for the maximum eosinophil count and symptom and endoscopy score, respectively, $P<0.0001$).

DISCUSSION

Eosinophilic esophagitis is a disorder of the esophagus which is becoming increasingly recognized (8, 14, 16, 17, 32–35). The annual incidence of the condition has been estimated at 1 in 10,000 children (35), but even this number may be an underestimate. The pathogenesis of EE is still poorly understood; allergic and abnormal host immunologic responses have been suggested. Therapeutic treatment options for EE have included dietary restriction/elemental diet, systemic and topical corticosteroids (2, 22–30). There is, however, presently no topical steroid designed for esophageal drug therapy. Twice daily ingested fluticasone propionate administered through an MDI is currently the most widely accepted topical therapy for EE. This therapy, however, may be particularly problematic for younger children and those with developmental delay who are unlikely to utilize the puff and swallow technique effectively (36). In our study, 10 of 13 children who were under the age of 5 and/or had developmental delay were *responders* to OVB therapy. The 3 *nonresponders* still demonstrated a 50–75% reduction in esophageal eosinophil count; all had symptomatic improvement and 2 had endoscopic improvement. In addition to this, of the 5 children (ages 3–9 yr) who previously failed to respond to swallowed fluticasone propionate therapy, 3 had pan-esophageal histologic normalization with OVB and the other 2 had >75% reduction in esophageal eosinophil count.

Our data suggest that following OVB therapy there is a strong correlation between the fall in esophageal eosinophil levels and the improvement in the endoscopy and symptom score. This suggests that our scoring tools are useful clinical measures in pediatric EE but further prospective studies will need to be done in order to validate these tools. Eighteen (90%) of our patients, including the *partial responder* and one *nonresponder*, had improved endoscopy scores and all symptomatic children had improved symptom scores. This may be because the *partialresponder* and even

Table 4. Symptom Score, Pre- and Post-Viscous Budesonide Therapy for Different Response Categories. Maximum Total Score Is 14 and Maximum for Each Category Is 2. Standard Error of Mean Shown in Paratheses

	Total Score Mean (SEM)		Heartburn		Pain		Nausea/Vomiting		Dysphagia		Nocturnal Wakening		Anorexia		GI Bleed	
Response Category	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Responders N = 16	4.2 (0.6)	0.75** (0.3)	1 (0.2)	0.1** (0.1)	0.8 (0.2)	0.2* (0.1)	1.4 (0.2)	0.1** (0.1)	0.2 (0.1)	0.1 (1)	0.2 (0.2)	0 (0)	0.6 (0.2)	0.3 (0.2)	None	None
Partial responder N = 1	6	2	2	1	2	1	2	0	0	0	0	0	0	0	None	None
Nonresponders N = 3	5.5* (2.5)	0.5* (0.5)	1.5 (0.5)	0.5 (0.5)	1.5 (0.5)	0 (0)	1.5 (0.5)	0 (0)	1 (1)	0 (0)	0	0	0	0	None	None

*$P < 0.05$; **$P < 0.001$; categories without asterisks do not reach statistical significance.

Figure 2. Distal esophageal image of patient with eosinophilic esophagitis (Olympus P160 endoscope) showing pallor, lichenification of the mucosa with linear furrowing (arrow). Following treatment with viscous budesonide, the esophagus appears normal (lower).

the 3 *nonresponders* had a 50–75% reduction in their highest esophageal eosinophil count following OVB treatment. In a few patients with EE, the correlation between symptom severity and esophageal eosinophilia does not always appear to be so clear and some patients with high eosinophil counts may in fact be entirely asymptomatic. Two initially symptomatic children (ages 7 and 13, Table 1) were asymptomatic before budesonide therapy despite having continued esophageal eosinophilic infiltration (80–120 eos/hpf). One child was a histologic *nonresponder* to elimination diet and the other to topical fluticasone propionate with PPI therapy, both for 3 months. These two children remained asymptomatic during budesonide therapy. This disassociation between symptoms and histologic disease is not unique to these two study patients. In our practice we have treated adolescents who, having initially responded symptomatically and histologically to ingested fluticasone propionate, became noncompliant to therapy, claimed to be asymptomatic, but on routine follow-up evaluation had endoscopic and histologic recurrence of disease. The exact reason for this remains unclear. Children may become accustomed to their symptoms and not complain. Alternatively, they may conceal their symptoms because of an unwillingness to continue therapy or fear of undergoing further tests such as endoscopy. Another possibility is that eosinophilic infiltration may not always cause symptoms, even within the same individual. Whereas this could explain why some patients only complain of symptoms if esophageal stricturing occurs, it still remains unclear as to whether asymptomatic children with esophageal eosinophilia need to be treated.

Most patients with EE are thought to have allergy-mediated disease, triggered by food and/or aeroallergens (2–4). However, 20% of our study patients had no evidence of IgE-mediated sensitization to foods or aeroallergens, and this concurs with other reported estimates of EE occurring in nonatopic individuals (17, 21, 35). Skin and patch testing can suggest causative food allergens in over half of the patients with EE, but not all will respond symptomatically or histologically to dietary restrictions (22). Amino acid-based formulas have been shown to be effective (2, 24, 37), but many children find the formula nonpalatable and often require feeding through a nasogastric or gastrostomy tube. In addition, after reintroducing new food to children on elemental diets, patients require regular repeat UGI endoscopy to confirm continued control of inflammation. Our study shows that children with EE, both with and without identifiable food/aero allergies respond well to OVB therapy and most are able to tolerate entirely normal diets. The dosing of OVB was based upon the therapeutic recommendations for asthmatic children. Most of our patients responded to 1 mg daily, but 2 patients needed 2 mg/day before a response was seen. The optimum dosing of viscous budesonide is still to be established. All patients tested, including those taking OVB 2 mg daily, had normal morning cortisol levels and were therefore unlikely to have significant adrenal suppression. This may be because budesonide absorbed intestinally undergoes rapid hepatic metabolism.

Although there are conflicting data from pediatric and adult studies, with reports of negative 24-h pH studies in children with EE, many patients will have at least a partial symptomatic response to acid-suppression therapy (1, 7, 17, 30, 38). Acid-suppression therapy alone will not, however, significantly alter the histologic findings, and persisting esophageal eosinophilia may ultimately lead to esophageal narrowing in 10–30% of cases (14, 18, 20, 21). This lack of histologic response to PPI therapy in patients with EE was confirmed in 10 of our study patients. We also noted that before starting all patients on OVB therapy, eosinophils were more abundant and BZH more prominent in distal, as compared

with mid- and proximal esophageal, biopsies (80, 53, and 43 eos/hpf, respectively, for tissue eosinophils and 95%, 75%, and 65% of biopsies for BZH, respectively). The reason for this distal predominance is unclear, but most likely supports the argument that GER does coexist with EE, particularly as BZH and mild tissue eosinophilia also occur in reflux esophagitis. Therefore, all patients treated with OVB also received acid-suppression therapy.

Our data suggest that OVB is an effective and safe treatment for young children with proven EE. It may have advantages over other therapies in that it is palatable, its volume (8–12 mL) provides pan-esophageal mucosal coverage, and it requires only once daily administration Larger placebo-controlled clinical trials would provide more information about dosing, efficacy, and long-term safety of this treatment.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Eosinophilic esophagitis (EE) causes symptoms that may mimic gastroesophageal reflux disease (GERD).
- EE responds to elimination diet and to twice daily fluticasone propionate.
- Young children may have difficulty taking these therapies.

What Is New Here

- Oral viscous budesonide (OVB) is safe, effective therapy for EE in children.
- OVB is a liquid, taken once daily, which has pan-esophageal coverage.
- OVB therapy will improve symptoms, endoscopic and histologic abnormalities seen in EE.

Reprint requests and correspondence: Ranjan Dohil, M.D., UCSD Medical Center, Hillcrest, 200 West Arbor Dr. San Diego, CA 92103-8450.

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CONFLICT OF INTEREST

Guarantor of the article: Dr. Ranjan Dohil, M.D.
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