

CLINICAL—ALIMENTARY TRACT

Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial



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BACKGROUND AND AIMS: Topical steroid treatments for eosinophilic esophagitis (EoE) include swallowed fluticasone from a multi-dose inhaler (MDI) or oral viscous budesonide (OVB) slurry, but the 2 have never been compared. We assessed whether OVB was more effective than MDI for initial treatment of patients with EoE. **METHODS:** In a double-blind, double-dummy trial, patients with a new diagnosis of EoE were randomly assigned to groups given 8 weeks of either OVB (1 mg/4 mL) twice daily plus a placebo inhaler (n = 56) or fluticasone MDI (880 µg) twice daily plus a placebo slurry (n = 55). Primary outcomes were post-treatment maximum eosinophil counts per high-power field (eos/hpf) and a validated dysphagia score (dysphagia symptom questionnaire [DSQ]) at week 8. Secondary outcomes included endoscopic severity (validated EoE endoscopic reference score), histologic response (<15 eos/hpf), and safety. **RESULTS:** In a modified intention-to-treat analysis, the subjects had baseline peak eosinophil counts of 73 and 77 eos/hpf in the OVB and MDI groups, respectively, and DSQ scores of 11 and 8. Post-treatment eosinophil counts were 15 and 21 in the OVB and MDI groups, respectively (P = .31), with 71% and 64% achieving histologic response (P = .38). DSQ scores were 5 and 4 in the OVB and MDI groups (P = .70). Similar trends were noted for post-treatment total EoE endoscopic reference scores (2 vs 3; P = .06). Esophageal candidiasis developed in 12% of patients receiving OVB and 16% receiving MDI; oral thrush was observed in 3% and 2%, respectively. **CONCLUSIONS:** In a randomized clinical trial, initial treatment of EoE with either OVB or fluticasone MDI produced a significant decrease in esophageal eosinophil counts and improved dysphagia and endoscopic features. However, OVB was not superior to MDI, so either is an acceptable treatment for EoE. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02019758) ID NCT02019758.

Keywords: Comparative-Effectiveness Study; Drugs; Steroids; Therapy.

symptoms of esophageal dysfunction.¹ In adolescents and adults, dysphagia symptoms predominate and are due to inflammation leading to progressive esophageal fibrosis, strictures, and narrowing.² The incidence and prevalence of EoE are rapidly rising, and the disease is now the most common cause of food impaction, with health care-related costs approaching \$1 billion/year.^{2,3}

Corticosteroids are currently the first-line pharmaceutical treatment option for patients with EoE who do not respond to proton pump inhibitor (PPI) therapy.⁴ Because there are no Food and Drug Administration–approved medications for EoE, asthma preparations, such as fluticasone in a multi-dose inhaler (MDI) or aqueous budesonide, are used. These medications are swallowed rather than inhaled, to coat the esophagus and provide a topical anti-inflammatory effect. For fluticasone MDI, patients puff the medication into their mouth and then swallow it.^{5–8} For aqueous budesonide, patients mix the liquid into a slurry with a sugar substitute, such as sucralose; this has been termed *oral viscous budesonide* (OVB).^{9,10} While both medications are effective for decreasing levels of esophageal eosinophilia,^{6–15} there are no clinical trials directly comparing the 2 treatments. This comparison is a key question because the amount of time a medication contacts the esophagus has been shown to directly correlate with histologic response in EoE.¹² Meta-analyses and retrospective studies suggest that viscous budesonide may have a more robust effect than fluticasone,^{16–18} and new esophageal-specific steroid formulations are under development for EoE, including one that has recently been approved in Europe.^{14,15} However, while OVB may provide increased esophageal contact time,¹² it is not commercially available and involves increased patient or pharmacy effort to mix, as well as added cost. It is unknown whether this

Abbreviations used in this paper: DSQ, dysphagia symptom questionnaire; EoE, eosinophilic esophagitis; eos/hpf, eosinophil counts per high-power field; EREFS, EoE Endoscopic Reference Score; MDI, multi-dose inhaler; OVB, oral viscous budesonide; PPI, proton pump inhibitor.

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Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated condition defined by abnormal infiltration of eosinophils into the esophagus and

WHAT YOU NEED TO KNOW**BACKGROUND AND CONTEXT**

Topical steroid treatments for eosinophilic esophagitis (EoE) include swallowed fluticasone from a multi-dose inhaler (MDI) and oral viscous budesonide (OVB) slurry. While both medications have been reported to be effective, the two have never been prospectively compared.

NEW FINDINGS

Treatment of EoE with either fluticasone MDI or slurry comparably improved esophageal eosinophil counts, dysphagia symptoms, and endoscopic features. Esophageal candidiasis was seen in 12% of the OVB group and 16% of MDI, but all were asymptomatic and detected at the post-treatment endoscopy.

LIMITATIONS

Single center study; Strictures were present in half of the study population, and dilation was allowed as clinically indicated, so symptom improvements may reflect both the medications and the esophageal dilation.

IMPACT

Both fluticasone slurry and MDI are effective treatments for EoE in patients who have not responded to proton pump inhibitors. The decision to use one over another may be based on patient or provider preference, ease of administration for a given patient, convenience, and cost.

formulation is more effective than fluticasone MDI for initial treatment of EoE.

We hypothesized that subjects treated with budesonide would have significantly lower post-treatment eosinophil counts and dysphagia symptom scores than subjects treated with fluticasone. The aim of this study, therefore, was to determine whether OVB is more effective than swallowed fluticasone MDI for improving esophageal eosinophil counts and symptoms of dysphagia for adult patients with EoE who did not respond to PPI therapy.

Methods

Study Design and Participants

We conducted a randomized, double-blind, double-dummy, parallel-arm, single-center, superiority clinical trial, from 2014 to 2018. The study was approved by the University of North Carolina Institutional Review Board, registered at ClinicalTrials.gov (NCT02019758), performed in accordance with the Declaration of Helsinki, and reported per CONSORT (Consolidated Standards of Reporting Trials).

Patients aged 16–80 years were eligible if they had a new diagnosis as EoE as per consensus guidelines at the time of the study design.^{19,20} Specifically, cases had to have dysphagia or other symptoms of esophageal dysfunction, persistent esophageal eosinophilia (≥ 15 eosinophils in at least 1 high-power field [eos/hpf]) after 8 weeks of treatment with a twice daily PPI, and other competing causes of esophageal eosinophilia excluded. A symptom threshold was not required for study entry. Patients were excluded if they had concomitant eosinophilic gastroenteritis; swallowed/topical steroids for EoE or

systemic steroids for any condition within the 4 weeks before baseline endoscopy; inability to pass a standard 9-mm upper endoscope due to esophageal narrowing or stricturing; previous esophageal surgery; esophageal or gastric cancer; esophageal varices, inability to stop anticoagulation, or active gastrointestinal bleeding; medical instability that precluded endoscopy; inability to read or understand English; or pregnancy. Esophageal dilation, using either balloons or bougies, was allowed during the study (at either the baseline or post-treatment endoscopy, or both) as clinically indicated at the discretion of the endoscopist. A diameter of 16–18 mm was the ultimate goal, though this may not have been achieved during this study.

Masking, Randomization, Interventions, and Outcomes

Subjects, investigators, endoscopists, statisticians, and study staff were all masked as to treatment allocation. The only unblinded person was the investigational pharmacist who was responsible for allocation of study medication. After eligibility was confirmed, informed consent obtained, and baseline measures collected, patients were randomized in 1:1 fashion to 2 treatment arms using a blocked randomization protocol with computer-generated variable block sizes. In the first arm, subjects were treated with OVB + a placebo inhaler. The OVB slurry preparation consisted of 1 mg/4 mL aqueous budesonide with 10 g of sucralose, administered twice daily,^{9,10,12,20} and was compounded and provided by the University of North Carolina investigational pharmacy premixed to all patients to ensure a consistent formulation. Patients also swallowed 4 puffs from a masked placebo inhaler twice daily after receiving verbal and written instructions on how to do so. In the second arm, subjects were treated with fluticasone MDI + a placebo slurry. The fluticasone dose was 880 μg twice daily, as 4 puffs of a 220 μg inhaler; the same instructions for use were provided.^{7,8,20} Patients also took 4 mL twice daily of a placebo slurry of sucralose identical in consistency and taste to that of the active treatment. Doses were selected based on the published guidelines and available efficacy data at the time this study was designed.^{6,8,10,11,20} For both arms, subjects were instructed to take the slurry first, the MDI 15 minutes later, and then nothing by mouth for an additional 30 minutes. This schedule was based on previously published esophageal emptying data for OVB, demonstrating that the half-life for OVB in the esophagus was < 2 minutes,¹² so interaction between slurry and inhaler would not be a concern. For both arms, the treatment period was 8 weeks, at which time endoscopy was repeated and outcomes measures assessed ([Supplementary Figure 1](#)). There was no placebo arm, given the extensive previous data demonstrating both of these treatments to be superior to placebo.¹⁶ We therefore sought to compare the 2 active agents to determine which was more effective. Of note, no dietary changes or changes in baseline PPI medication dose were allowed during the study period.

The primary outcome was the post-treatment peak eosinophil count (eos/hpf; hpf area = 0.24 mm²). Eosinophil counts were determined by the study pathologist (JTW) both for the screening (baseline) and post-treatment examinations using a previously validated protocol.^{21,22} In brief, 4 esophageal biopsies were obtained from both the distal (3 cm above the gastroesophageal junction) and proximal (15 cm above the

junction) esophagus to maximize sensitivity of detecting eosinophils.²³ On each biopsy fragment, 5 hpfs were examined and the overall peak eosinophil count was determined from the field deemed to be most inflamed from all esophageal levels and all hpfs.

The co-primary outcome was the dysphagia score, as measured by the Dysphagia Symptom Questionnaire (DSQ).²⁴ This daily symptom diary is a validated and responsive patient-reported outcome consisting of 3 questions that assess the frequency and severity of dysphagia, with a 24-hour recall. The first question asks if any solid food has been eaten that day. If the answer is yes, the second and third questions are asked and scored. The second question asks whether food has gone down slowly or has stuck in the chest. The third question asks whether anything had to be done to make the food go down or get relief, and provides 5 options, ranging from it getting better spontaneously to having to seek medical care. The score ranges from 0 to 84, with higher scores indicating more severe symptoms.¹⁵ Symptom data were collected and the DSQ calculated over 2-week periods to minimize the effect of symptom variation: 2 weeks immediately before randomization and the 2 weeks immediately before the follow-up endoscopy.

Prespecified secondary outcomes included endoscopic findings of EoE as measured with the validated EoE Endoscopic Reference Score (EREFS). This score quantifies 5 key endoscopic findings: exudates (scored 0–2), esophageal rings (scored 0–3), edema (scored 0–1), furrows (scored 0–2), and strictures (scored 0–1).²⁵ The EREFS score ranges from 0 to 9, with higher scores indicating more severe endoscopic findings. We also analyzed levels of histologic response, including peak counts of <15 eos/hpf, <5 eos/hpf, and <1 eos/hpf,^{26,27} and measured dysphagia severity with the EoE Symptom Activity Index (EEsAI), a validated patient-reported outcome with a 7-day recall that also incorporates dietary avoidance and modification (scores range from 0 to 100, with higher scores indicating more severe symptoms; a score <20 indicates symptom remission).²⁸ Medication compliance and adverse events were also assessed.

Statistical Analysis

Characteristics of the study groups were summarized with descriptive statistics. The mean post-treatment peak eosinophil counts and DSQ scores were compared between the OVB and MDI groups using a 2-sample *t* test. The pre- and post-treatment peak counts and scores were also compared within study groups using a paired *t* test. For secondary outcomes, post-treatment means were compared with *t* tests, and proportions were compared with χ^2 between groups, and with McNemar's test within groups. We performed post-hoc analyses to explore predictors of treatment response, examine histologic differences in the proximal and distal esophagus, and evaluate all key outcomes as stratified by baseline esophageal dilation. All analyses were by modified intention-to-treat, as follow-up endoscopy was required for primary outcome assessment; therefore, the analysis cohort consisted of all those with baseline and week-8 endoscopies.

The sample size calculation was based on estimates of histologic improvement from topical steroids in EoE.^{6,7,10,12,13,29–31} We estimated that baseline peak eosinophil counts would be 80 eos/hpf, and hypothesized that post-treatment counts would be 10 eos/hpf in the OVB arm and

Table 1. Baseline Characteristics of All Randomized Study Subjects

Characteristics	Budesonide (n = 65)	Fluticasone (n = 64)
Age, y, mean \pm SD	36.2 \pm 19.1	39.0 \pm 14.5
Male, n (%)	40 (62)	44 (69)
White, n (%)	63 (97)	63 (98)
Body mass index, kg/m ² , mean \pm SD	26.2 \pm 5.9	27.6 \pm 6.8
Symptoms		
Dysphagia, n (%)	62 (95)	60 (94)
Length of dysphagia, y, mean \pm SD	11.2 \pm 9.9	10.4 \pm 10.0
Heartburn/reflux, n (%)	36 (55)	36 (56)
Chest pain, n (%)	16 (25)	18 (28)
Abdominal pain, n (%)	16 (25)	15 (23)
Nausea, n (%)	14 (22)	7 (11)
Vomiting, n (%)	9 (14)	14 (22)
Any atopic condition, n (%)	46 (71)	50 (78)
Asthma	19 (30)	16 (25)
Eczeema	16 (25)	9 (14)
Seasonal allergies/allergic rhinitis	37 (57)	40 (63)
Food allergies ^a	25 (40)	27 (42)
Endoscopic features		
Total EREFS score, mean \pm SD	4.7 \pm 1.8	4.7 \pm 1.9
EREFS component scores, mean \pm SD		
Exudates	0.95 \pm 0.65	0.89 \pm 0.69
Rings	1.25 \pm 0.94	1.25 \pm 0.80
Edema	0.82 \pm 0.39	0.81 \pm 0.39
Furrows	1.12 \pm 0.45	1.17 \pm 0.55
Stricture	0.62 \pm 0.49	0.58 \pm 0.50
Stricture size, mm	12.4 \pm 3.1	12.6 \pm 2.8
Dilation required at baseline examination, n (%)	34 (52)	35 (54)
Peak overall eosinophil count, eos/hpf, mean \pm SD	74.1 \pm 48.2	72.5 \pm 59.1

^aPatient self-report; could include an overt reaction or sensitization.

20 eos/hpf in the MDI arm. To detect this difference with a power of 0.9, 53 subjects per arm were needed, and assuming a 15% dropout rate 15%,¹² we planned to enroll 61 subjects in each arm, for a total of 122. This sample size also provided a power of 0.9 to detect a clinically significant DSQ difference equivalent to having 1 fewer day of dysphagia per week.²⁴

Data were collected and the database was managed by the investigators. All authors had access to the study data and reviewed and approved the final manuscript. All analyses for the primary and prespecified secondary outcomes were performed masked to allocation and before breaking the study blind.

Results

Patient Flow and Baseline Characteristics

Of 183 patients screened, 129 met eligibility requirements and were randomized, 65 to OVB and 64 to fluticasone MDI (Supplementary Figure 2). One subject in

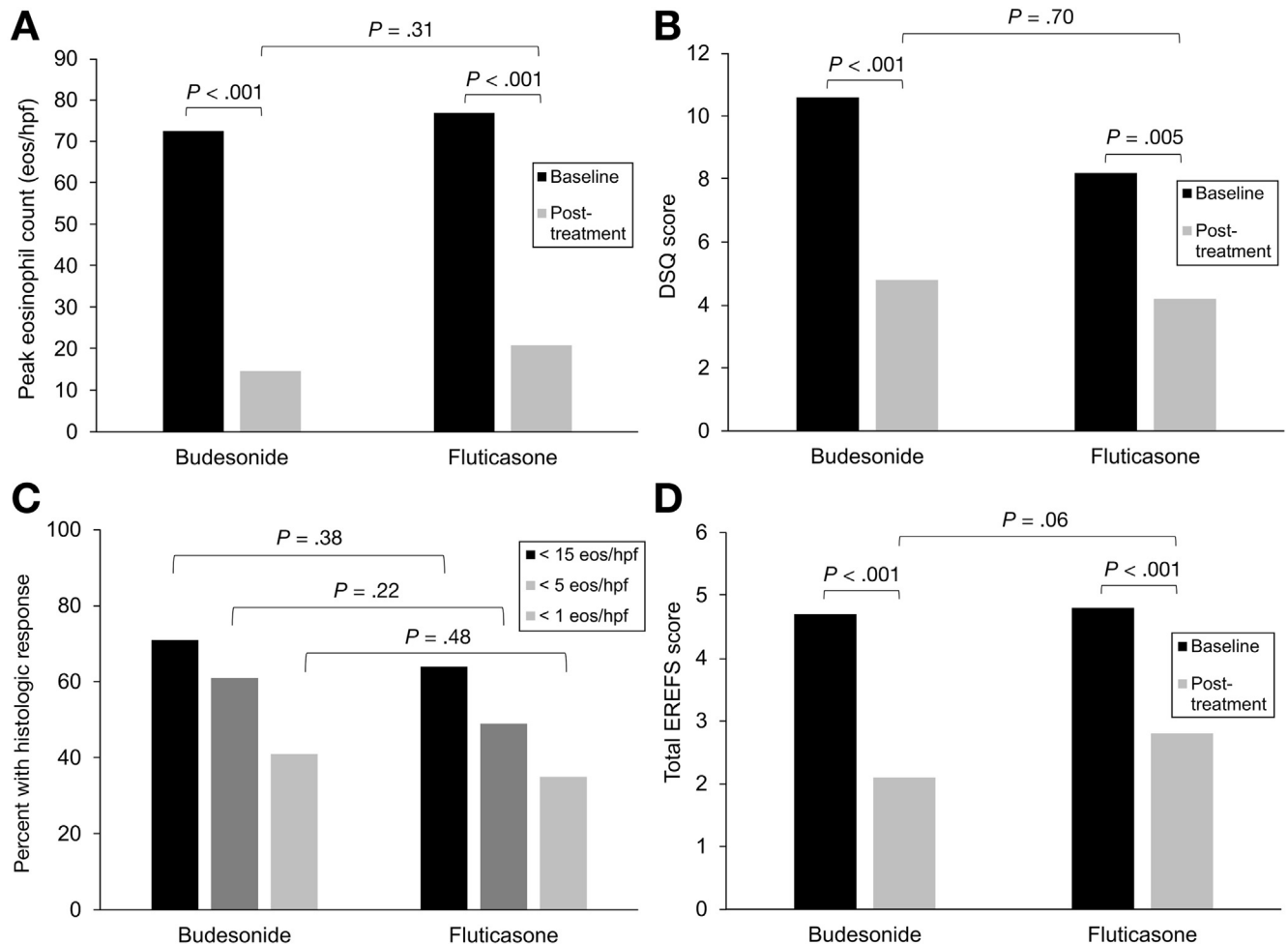


Figure 1. Study outcome measures. (A) Primary outcome of peak eosinophil count. (B) Co-primary outcome of the DSQ score. (C) Secondary outcome of histologic response thresholds of <15, <5, and <1 eos/hpf. (D) Secondary outcome of the EoE Endoscopic Reference Score.

each group did not receive the intervention after randomization, and 8 in each group were lost to follow-up and did not undergo the week-8 endoscopy. Overall, the groups were well matched (Table 1) and medication compliance was 86% overall.

Primary Outcomes

The baseline peak eosinophil counts were 72.6 ± 45.6 in the OVB group and 76.9 ± 62.3 in MDI, and after 8 weeks of treatment the follow-up counts decreased to 14.7 ± 29.0 and 20.9 ± 34.3 , respectively ($P = .31$) (Figure 1A, Table 2). There was no difference in the change in peak eosinophil count from baseline between OVB and MDI (-57.9 ± 55.9 vs -56.1 ± 55.6 ; $P = .57$).

The baseline DSQ scores were 10.6 ± 9.3 in OVB and 8.2 ± 9.9 in MDI. After 8 weeks of treatment, the follow-up scores decreased to 4.8 ± 7.3 and 4.2 ± 7.5 , respectively ($P = .70$) (Figure 1B, Table 2). There was no difference in the change in DSQ score from baseline between OVB and MDI (-5.8 ± 9.6 vs -4.0 ± 8.3 ; $P = .37$). Similar findings were noted for the EoE Symptom Activity Index score (Table 2). Findings for the primary outcomes did not change

substantially after stratifying for esophageal dilation at baseline (Supplementary Table 1).

Secondary Outcomes, Predictors of Response, and Adverse Events

Histologic response rates were similar between OVB and MDI. Overall, 71% in OVB and 64% in MDI achieved <15 eos/hpf ($P = .38$), and there were no differences in OVB vs MDI with different response thresholds (Figure 1C). Histologic outcomes were similar when proximal and distal esophageal locations were considered separately (Supplementary Table 2).

The baseline EREFS scores were 4.7 ± 1.8 in OVB and 4.8 ± 2.0 in MDI. After 8 weeks of treatment, the follow-up scores decreased to 2.1 ± 1.7 and 2.8 ± 2.2 , respectively ($P = .06$) (Figure 1D, Table 2). There was no difference in the change in EREFS score from baseline between OVB and MDI (-2.6 ± 1.8 vs -1.9 ± 2.0 ; $P = .07$). Findings were similar for both inflammatory and fibrotic components of the EREFS classification, and all individual components improved with the exception of

Table 2. Key Primary and Secondary Histologic, Symptom, and Endoscopic Outcomes

Outcomes	Budesonide	Fluticasone	P value
Histologic outcomes	n = 56	n = 55	
Peak eosinophil count			
Baseline, eos/hpf, mean ± SD	72.6 ± 45.6	76.9 ± 62.3	.67
Post-treatment, ^a eos/hpf, mean ± SD	14.7 ± 29.0	20.9 ± 34.3	.31
P value (paired pre/post treatment)	<.001	<.001	
Absolute change in count, eos/hpf, mean ± SD	-57.9 ± 55.9	-56.1 ± 55.6	.57
Percentage change in count, eos/hpf, mean ± SD	-70.8 ± 64.1	-71.7 ± 44.1	.93
Histologic response thresholds, n (%)			
<15 eos/hpf	40 (71)	35 (64)	.38
<5 eos/hpf	34 (61)	27 (49)	.22
<1 eos/hpf	23 (41)	19 (35)	.48
Symptom outcomes			
DSQ score	n = 46	n = 38	
Baseline, mean ± SD	10.6 ± 9.3	8.2 ± 9.9	.26
Post-treatment, ^a mean ± SD	4.8 ± 7.3	4.2 ± 7.5	.70
P value (paired pre/post-treatment)	<.001	.005	
Change in DSQ	-5.8 ± 9.6	-4.0 ± 8.3	.37
EEsAI score	n = 32	n = 38	
Baseline, mean ± SD	36.5 ± 23.3	35.9 ± 20.4	.91
Post-treatment, mean ± SD	22.1 ± 18.9	28.0 ± 20.4	.22
P value (paired pre/post-treatment)	<.001	.005	
Change in EEsAI, mean ± SD	-14.4 ± 15.7	-7.9 ± 16.2	.10
EEsAI in remission, ^b n (%)			
Baseline	11 (29)	11 (26)	.73
Post-treatment	17 (43)	18 (39)	.75
Endoscopic outcomes	n = 56	n = 55	
Total EREFS score			
Baseline, mean ± SD	4.7 ± 1.8	4.8 ± 2.0	.89
Post-treatment, mean ± SD	2.1 ± 1.7	2.8 ± 2.2	.06
P value (paired pre/post-treatment)	<.001	<.001	
Change in EREFS, mean ± SD	-2.6 ± 1.8	-1.9 ± 2.0	.07

EEsAI, EoE Symptom Activity Index.

^aCo-primary outcomes.

^bDefined as a score <20.

strictures (Supplementary Table 3). Findings for the secondary outcomes also did not change substantially after stratifying for baseline dilation (Supplementary Table 1).

Given that histologic improvement was similar in the OVB and fluticasone MDI groups, we examined predictors of histologic response (defined as <15 eos/hpf) for all subjects in the modified intention-to-treat cohort (n = 111). Compared to histologic non-responders, responders were somewhat younger, had a lower BMI, more eczema, a lower total EREFS score, less esophageal narrowing, and lower peak eosinophil counts (Table 3). On multivariable logistic regression, younger age, lower BMI, presence of eczema, and absence of esophageal narrowing were independently associated with treatment response (Supplementary Table 4).

Overall, both OVB and fluticasone MDI were well tolerated. When analyzing all subjects who were randomized (n = 129), 10 (15%) in the OVB group and 15 (23%) in the MDI group had an adverse event (Table 4). Esophageal candidiasis was most common (12% in OVB and 16% in MDI), but all were asymptomatic and detected at the post-treatment endoscopy. There were 2 subjects in OVB and 1

in MDI who had oral candidiasis, and all of these episodes were symptomatic. There was 1 serious adverse event, a food impaction that required urgent endoscopy in a subject in the MDI group who had stopped taking medications during the 8-week treatment phase.

Discussion

Swallowed/topical corticosteroids are the recommended pharmacologic treatment for EoE patients who have not responded to PPIs,^{19,20} and clinical trials have shown that compared to placebo, both OVB and fluticasone MDI are effective.^{6-8,10,13-15} However, there have been no head-to-head trials of these 2 medications. We conducted a randomized, double-blind, double-dummy clinical trial to determine if budesonide was more effective than swallowed fluticasone MDI for initial treatment of patients with EoE. We found that while both medications improved esophageal eosinophil counts, symptoms of dysphagia, and endoscopic severity, improvements from OVB were not statistically superior to those seen with fluticasone, indicating that either medication could be an acceptable choice for first-line treatment.

Table 3. Predictors of Histologic Treatment Response

Variable	Non-responders (≥ 15 eos/hpf) (n = 36)	Responders (< 15 eos/hpf) (n = 75)	P value
Age, y, mean \pm SD	35.2 \pm 14.1	40.8 \pm 15.5	.07
Male, n (%)	25 (69)	49 (65)	.67
White, n (%)	33 (92)	74 (99)	.06
BMI, kg/m^2 , mean \pm SD	28.8 \pm 7.1	26.2 \pm 6.1	.05
Length of dysphagia, y, mean \pm SD	10.0 \pm 1.7	11.0 \pm 9.8	.63
DSQ score, mean \pm SD	10.4 \pm 11.8	8.8 \pm 9.3	.48
EEsAI score, mean \pm SD	40.1 \pm 27.0	33.3 \pm 20.1	.18
Any atopic condition, n (%)	26 (72)	56 (75)	.78
Asthma	13 (36)	18 (24)	.18
Eczema	3 (8)	18 (24)	.05
Seasonal allergies/allergic rhinitis	22 (64)	45 (60)	.69
Food allergies ^a	16 (44)	31 (41)	.76
Endoscopic features			
Total EREFS score, mean \pm SD	5.30 \pm 1.62	4.47 \pm 1.93	.03
Inflammatory EREFS score, mean \pm SD	3.33 \pm 0.93	2.61 \pm 1.25	.003
Fibrotic EREFS score, mean \pm SD	1.97 \pm 1.06	1.85 \pm 1.02	.57
EREFS components, mean \pm SD			
Exudates	1.22 \pm 0.64	0.76 \pm 0.61	<.001
Rings	1.44 \pm 0.81	1.21 \pm 0.83	.17
Edema	0.94 \pm 0.23	0.75 \pm 0.44	.01
Furrows	1.17 \pm 0.38	1.11 \pm 0.56	.56
Stricture ^b	0.53 \pm 0.51	0.64 \pm 0.48	.26
Stricture size, mm, mean \pm SD	11.6 \pm 2.3	13.0 \pm 3.0	.07
Narrowing, ^b n (%)	17 (47)	12 (16)	<.001
Dilation required at baseline examination, n (%)	19 (53)	41 (55)	.85
History of esophageal dilation, n (%)	20 (56)	39 (52)	.73
Pull sign positive, n (%)	21 (64)	32 (49)	.18
Peak overall eosinophil count, eos/hpf, mean \pm SD	90.5 \pm 68.4	67.2 \pm 44.7	.03
Proximal peak	58.3 \pm 56.7	33.2 \pm 39.2	.008
Distal peak	75.8 \pm 65.4	59.7 \pm 43.6	.13
Degranulation, n (%)	28 (78)	50 (67)	.23
Microabscess, n (%)	32 (89)	55 (73)	.06
Spongiosis, n (%)	34 (94)	65 (87)	.22
Lamina propria fibrosis, n (%)	28 (88)	39 (80)	.36

EEsAI, EoE Symptom Activity Index.

^aPatient self-report; could include an overt reaction or sensitization.

^bStricture is defined as a focal impingement in the esophageal lumen; narrowing is defined as a more diffuse decrease in esophageal caliber.

Given the number of patients with EoE, and the toll of the disease both in quality of life and health care expenditures, definition of optimal treatment of this condition is essential. There has long been discussion in the literature over whether one topical steroid is preferable to another in EoE. Because a viscous solution would be easier to swallow and coat the esophagus, such a preparation might be more efficacious than delivering the medication to the esophagus from an MDI. A meta-analysis and retrospective data support this hypothesis.^{16–18} A previous clinical trial using medication labeled with radioactive tracer compared OVB with budesonide that was nebulized and then swallowed, and measured esophageal contact time for each medication delivery technique.¹² Overall OVB was more effective than nebulized/swallowed budesonide (post-treatment peak eosinophil count of 11 vs 89 eos/hpf) in this study. Additionally, higher mucosal contact time, as measured by nuclear scintigraphy, correlated with decrease in eosinophil

count, regardless of the medication formulation. With this realization, there has been a strong interest in developing esophageal-specific topical steroid formulations for EoE that maximize esophageal mucosal contact time, including a suspension of budesonide^{13,15} and oral dissolving tablets of budesonide and fluticasone.^{14,32}

Why did the findings in this study not support our hypothesis that the OVB formulation would be superior? One possibility is that this study was not a pure comparison of formulation. To do this, we would have needed to test OVB against budesonide MDI, not fluticasone MDI. However, a budesonide MDI device is not commercially available, budesonide MDI has never been studied in EoE, and fluticasone MDI is most commonly used.³³ Therefore, this study made the clinically relevant comparison between the 2 most commonly used, and commercially available steroid therapies for this disease state. Based on the asthma literature and comparative pharmacology,

Table 4. Adverse Events

Variable	Budesonide (n = 65)	Fluticasone (n =64)
Adverse event, n (%)		
Esophageal candidiasis	8 (12)	10 (16)
Oral candidiasis	2 (3)	1 (2)
Food impaction	0 (0)	1 (2)
Sore throat	0 (0)	2 (3)
Chest pain	0 (0)	1 (2)
Pneumonia	0 (0)	1 (2)
Any adverse event, n (%)	10 (15)	15 (23)
Serious adverse event, n (%)	0 (0)	1 (2)

fluticasone is more potent than budesonide.^{34,35} It is possible, then, that even with less optimal delivery via MDI, the higher potency of fluticasone resulted in similar efficacy. Another possibility is that the timing of the active and “dummy” medication may have impacted efficacy. Subjects were instructed to take the slurry first and wait 15 minutes before using the inhaler, based on our prior data showing rapid esophageal emptying for a slurry.¹² However, if patients immediately used the MDI after the slurry, it is possible that any slurry remaining in the esophagus could have increased the fluticasone esophageal contact time. While we could not track the timing between each dose in each patient, we did observe similar histologic effects in both the proximal and distal esophagus for both medications. We performed a post-hoc analysis in the most compliant patients (>70% medication use), and the results were unchanged (data not shown). Finally, it is possible that these medications are both quite effective, and our study reflects that. In a recent meta-analysis, the pooled histologic response rate (at the 15 eos/hpf threshold) was 77% for OVB and 69% for fluticasone,¹⁶ very similar to the rates of 71% and 64% that we observed, though this meta-analysis included both observational studies and clinical trials. With these results, the decision to use OVB or MDI may come down to practical issues, including costs and insurance coverage. Patients may also have a preference as to convenience of mixing a slurry compared to having an inhaler at the ready, as well as ease of use in terms of swallowing a slurry vs swallowing a medication dispensed from an inhaler.

There are limitations to the present study. It was conducted at a single referral center, and though the general characteristics of the study population are similar to those reported for EoE cases in general (male predominance, white, and highly atopic), subjects had a long duration of symptoms before diagnosis. This resulted in a high burden of strictures, with half of patients needing esophageal dilation at baseline. It has been previously observed that patients who require dilation at baseline may have lower treatment response rates.³⁶ Because dilation was allowed at the baseline endoscopic examination, symptom assessments (which were done after the baseline endoscopy) likely reflected less severe dysphagia,

though results were largely unchanged after stratifying for baseline dilation, and similar proportions of subjects in each arm underwent dilation in each arm. Symptom scores were also lower than recently reported in a trial of a budesonide oral suspension because there was not a symptom threshold for entry into the present study,¹⁵ and there may have been some differences in the DSQ score calculation itself.²⁴ In addition, not all randomized patients completed the symptom measures, so symptom data should be interpreted with caution. A final limitation is that all patients in this study were treated with PPIs, as required by diagnostic guidelines at the time of the study design and conduct.^{19,20} The most recent diagnostic guidelines have removed the need for a PPI trial before diagnosis,³⁷ so the results of this study cannot be applied to EoE patients who have not previously undergone a PPI trial.

These limitations are countered by a number of strengths. This was a rigorously designed and conducted trial with a double-dummy design that has not previously been used in EoE trials. The study population is the largest included in a topical steroid trial to date, and consisted of newly diagnosed EoE cases undergoing their first treatment course with a topical steroid. Validated outcome metrics, including a patient-reported outcome (the DSQ)^{15,24} and an endoscopic severity scale (EREFS)²⁵ were used, and histologic outcomes were assessed by a single pathologist to minimize variability. This is also one of the only comparative effectiveness clinical trials in EoE, and the results have direct relevance to a large number of patients suffering from this increasingly common disease.

In conclusion, this randomized, double-blind, double-dummy clinical trial comparing OVB and fluticasone MDI for initial treatment of EoE showed that both medications significantly decreased esophageal eosinophil counts and improved dysphagia symptoms and endoscopic features. However, the swallowed slurry was not superior to MDI. This indicates that either OVB or fluticasone MDI are acceptable choices for initial EoE therapy. The decision to use one over another may be based on patient or provider preference, ease of administration for a given patient, convenience, and cost.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2019.03.014>.

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Conflicts of interest

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