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

Evan S. Dellon, MD MPH[1], **John T. Woosley, MD PhD**[2], **Ashley Arrington, BA**[1], **Sarah J. McGee, BA CCRC**[1], **Jacquelyn Covington, BA CCRP**[1], **Susan E. Moist, MPH CCRP**[1], **Jessica H. Gebhart, MSHS**[1], **Alexandra E. Tylicki, BA**[1], **Shiyan O. Shoyoye, BA**[1], **Christopher F. Martin, MPH**[1], **Joseph A. Galanko, PhD**[1], **John A. Baron, MD MS MSc**[1], and **Nicholas J. Shaheen, MD MPH**[1]

[1]Center for Esophageal Diseases and Swallowing, and Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology;

[2]Department of Pathology and Laboratory Medicine; University of North Carolina School of Medicine, Chapel Hill, NC

Abstract

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 two 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 (1mg/4mL) twice daily plus a placebo inhaler (n=56) or fluticasone MDI (880 mcg) 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.

Conclusion: 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 number NCT02019758)

Keywords

comparative-effectiveness study; drugs; steroids; therapy

Introduction

Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated condition defined by abnormal infiltration of eosinophils into the esophagus and 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 FDA-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," or OVB.[9,10] While both medications are effective for decreasing levels of esophageal eosinophilia,[6–15] there are no clinical trials directly comparing the two. 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, involves increased patient or pharmacy effort to mix, as well as added cost. It is unknown whether this 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 2014–2018. 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.

Patients age 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 one high-power field [eos/hpf]) after 8 weeks of treatment with a twice daily proton-pump inhibitor, 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 prior to baseline endoscopy; inability to pass a standard 9mm upper endoscope due to esophageal narrowing or stricturing; previous esophageal surgery; esophageal or gastric cancer; esophageal varices, inability to stop anticoagulation, or active GI 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 two 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 UNC investigational pharmacy pre-mixed 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 mcg twice daily, as 4 puffs of a 220 mcg 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 a concern.

For both arms, the treatment period was 8 weeks, at which time endoscopy was repeated and outcomes measures assessed (Supplementary Figure). 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 two 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=0.24mm^2). Eosinophil counts were determined by the study pathologist (JTW) both for the screening (baseline) and post-treatment exams 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 high-power fields were examined and the overall peak eosinophil count was determined from the field deemed to be most inflamed from all esophageal levels and all high-power fields.

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 (PRO) consisting of three 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 0–84, with higher scores indicating more severe symptoms.[15] Symptom data were collected and the DSQ calculated over two week periods to minimize the effect of symptom variation: two weeks immediately prior to randomization and the two weeks immediately prior to the follow-up endoscopy.

Pre-specified secondary outcomes included endoscopic findings of EoE, as measured with the validated EoE Endoscopic Reference Score (EREFS). This score quantifies five 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 0–9, 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 PRO with a 7-day recall that also incorporates dietary avoidance and modification (scores range from 0–100, with higher scores indicated more severe symptoms; a score <20 indicates symptom remission).[28] Medication compliance and adverse events (AEs) 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 two-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 chi-square 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 20 eos/hpf in the MDI arm. To detect this different with a power of 0.9, 53 subjects per arm were needed, and assuming a 15% drop-out rate 15%,[12] we planned to enroll 61 subjects in each arm, for a total or 122. This sample size also provided a power of 0.9 to detect a clinically significant DSQ difference equivalent to having one day less 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 pre-specified secondary outcomes were performed masked to allocation and prior to 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 (Figure 1). One subject in 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=0.31) (Figure 2A; 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=0.57).

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=0.70) (Figure 2B; 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=0.37). Similar findings were noted for the EEsAI 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=0.38), and there were no differences in OVB vs MDI with different response thresholds (Figure 2C). 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=0.06) (Figure 2D; 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=0.07). Findings were similar for both inflammatory and fibrotic components of the EREFS classification, and all individual components improved with the exception of 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 ITT 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 AE (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 AE, 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 two 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.

Given the number of patients with EoE, and the toll of the disease both in quality of life and healthcare 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 labelled 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 two most commonly used, and commercially available steroid therapies for this disease state. Based on the asthma literature and comparative pharmacology, 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 versus 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, highly atopic), subjects had a long duration of symptoms prior to 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 exam, 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 prior to 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 PRO (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

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

References

1. Furuta GT, Katzka DA. Eosinophilic Esophagitis. N Engl J Med 2015;373:1640–8. [PubMed: 26488694]

2. Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. Gastroenterology 2018;154:319–322.e3. [PubMed: 28774845]

3. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-Care Utilization, Costs, and the Burden of Disease Related to Eosinophilic Esophagitis in the United States. Am J Gastroenterol 2015;110:626–32. [PubMed: 25267327]

4. Dellon ES, Liacouras CA. Advances in Clinical Management of Eosinophilic Esophagitis. Gastroenterology 2014;147:1238–1254. [PubMed: 25109885]

5. Teitelbaum JE, Fox VL, Twarog FJ, Nurko S, Antonioli D, Gleich G, Badizadegan K, Furuta GT. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology 2002;122:1216–25. [PubMed: 11984507]

6. Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, Akers R, Cohen MB, Collins MH, Assa'ad AH, Aceves SS, Putnam PE, Rothenberg ME. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology 2006;131:1381–91. [PubMed: 17101314]

7. Alexander JA, Jung KW, Arora AS, Enders F, Katzka DA, Kephardt GM, Kita H, Kryzer LA, Romero Y, Smyrk TC, Talley NJ. Swallowed Fluticasone Improves Histologic but Not Symptomatic Responses of Adults with Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2012;10:742–9.e1. [PubMed: 22475741]

8. Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, Kramer RE, Collins MH, Stucke E, Mangeot C, Jackson WD, O'Gorman M, Abonia JP, Pentiuk S, Putnam PE, Rothenberg ME. Efficacy, Dose Reduction, and Resistance to High-dose Fluticasone in Patients with Eosinophilic Esophagitis. Gastroenterology 2014;147:324–33.e5. [PubMed: 24768678]

9. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral Viscous Budesonide: A Potential New Therapy for Eosinophilic Esophagitis in Children. Am J Gastroenterol 2007;102:2271–9. [PubMed: 17581266]

10. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral Viscous Budesonide Is Effective in Children With Eosinophilic Esophagitis in a Randomized, Placebo-controlled Trial. Gastroenterology 2010;139:418–29. [PubMed: 20457157]

11. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–37, 1537 e1. [PubMed: 20682320]

12. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, Ivanovic M, Chau A, Woosley JT, Madanick RD, Orlando RC, Shaheen NJ. Viscous Topical is More Effective than Nebulized Steroid Therapy for Patients with Eosinophilic Esophagitis. Gastroenterology 2012;143:321–324.e1. [PubMed: 22561055]

13. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2015;13:66–76 e3. [PubMed: 24907502]

14. Miehlke S, Hruz P, Vieth M, Bussmann C, von Arnim U, Bajbouj M, Schlag C, Madisch A, Fibbe C, Wittenburg H, Allescher HD, Reinshagen M, Schubert S, Tack J, Muller M, Krummenerl P, Arts J, Mueller R, Dilger K, Greinwald R, Straumann A. A randomised, double-blind trial

comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016;65:390–9. [PubMed: 25792708]

15. Dellon ES, Katzka DA, Collins MH, Hamdani M, Gupta SK, Hirano I, MPI10106-Investigators. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared with Placebo in Patients with Eosinophilic Esophagitis. Gastroenterology 2017;152:776–786.e5. [PubMed: 27889574]

16. Cotton CC, Eluri S, Wolf WA, Dellon ES. Six-Food Elimination Diet and Topical Steroids are Effective for Eosinophilic Esophagitis: A Meta-Regression. Dig Dis Sci 2017;62:2408–2420. [PubMed: 28608048]

17. Fable JM, Fernandez M, Goodine S, Lerer T, Sayej WN. Retrospective Comparison of Fluticasone Propionate and Oral Viscous Budesonide in Children With Eosinophilic Esophagitis. J Pediatr Gastroenterol Nutr 2018;66:26–32. [PubMed: 28489670]

18. Krishna SG, Kakati BR, Olden KW, Brown DK. Treatment of eosinophilic esophagitis: is oral viscous budesonide superior to swallowed fluticasone spray? Gastroenterol Hepatol (N Y) 2011;7:55–9. [PubMed: 21346855]

19. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.e6. [PubMed: 21477849]

20. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras C, Katzka DA. ACG Clinical Guideline: Evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. Am J Gastroenterol 2013;108:679–92. [PubMed: 23567357]

21. Dellon ES, Fritchie KJ, Rubinas TC, Woosley JT, Shaheen NJ. Inter- and intraobserver reliability and validation of a new method for determination of eosinophil counts in patients with esophageal eosinophilia. Dig Dis Sci 2010;55:1940–9. [PubMed: 19830560]

22. Rusin S, Covey S, Perjar I, Hollyfield J, Speck O, Woodward K, Woosley JT, Dellon ES. Determination of esophageal eosinophil counts and other histologic features of eosinophilic esophagitis by pathology trainees is highly accurate. Hum Pathol 2017;62:50–55. [PubMed: 28041975]

23. Gonsalves N, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. Gastrointest Endosc 2006;64:313–9. [PubMed: 16923475]

24. Dellon ES, Irani AM, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:634–42. [PubMed: 23837796]

25. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–95. [PubMed: 22619364]

26. Wolf WA, Cotton CC, Green DJ, Hughes JT, Woosley JT, Shaheen NJ, Dellon ES. Evaluation of histologic cutpoints for treatment response in eosinophilic esophagitis. J Gastroenterol Hepatol Research 2015;4:1780–87. [PubMed: 27110513]

27. Reed CC, Wolf WA, Cotton CC, Rusin S, Perjar I, Hollyfield J, Woosley JT, Shaheen NJ, Dellon ES. Optimal Histologic Cutpoints for Treatment Response in Patients With Eosinophilic Esophagitis: Analysis of Data From a Prospective Cohort Study. Clin Gastroenterol Hepatol 2018;16:226–233.e2. [PubMed: 28987502]

28. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, Haas NA, Romero Y, Hirano I, Alexander JA, Gonsalves N, Furuta GT, Dellon ES, Leung J, Collins MH, Bussmann C, Netzer P, Gupta SK, Aceves SS, Chehade M, Moawad FJ, Enders FT, Yost KJ, Taft TH, Kern E, Zwahlen M, Safroneeva E. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255–66 e21. [PubMed: 25160980]

29. Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci 2010;55:1313–9. [PubMed: 19533356]

30. Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, Lim JD, Steiner SJ, Gupta SK. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol 2008;6:165–73. [PubMed: 18237866]

31. Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. Am J Gastroenterol 2013;108:366–72. [PubMed: 23399553]

32. Hirano I, Schoepfer AM, Commer GM, Safroneeva E, Meltzer BA, Falk GW. A Randomized, Double-Blind, Placebo-Controlled Trial of a Fluticasone Propionate Orally Disintegrating Tablet in Adult and Adolescent Patients with Eosinophilic Esophagitis: A Phase 1/2A Safety and Tolerability Study. Gastroenterology 2017;152 (Suppl 1):S195.

33. Peery AF, Shaheen NJ, Dellon ES. Practice patterns for the evaluation and treatment of eosinophilic oesophagitis. Aliment Pharmacol Ther 2010;32:1373–82. [PubMed: 21050240]

34. Nielsen LP, Dahl R. Therapeutic ratio of inhaled corticosteroids in adult asthma. A dose-range comparison between fluticasone propionate and budesonide, measuring their effect on bronchial hyperresponsiveness and adrenal cortex function. Am J Respir Crit Care Med 2000;162:2053–7. [PubMed: 11112113]

35. Hubner M, Hochhaus G, Derendorf H. Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. Immunol Allergy Clin North Am 2005;25:469–88. [PubMed: 16054538]

36. Wolf WA, Cotton CC, Green DJ, Hughes JT, Woosley JT, Shaheen NJ, Dellon ES. Predictors of response to steroid therapy for eosinophilic esophagitis and treatment of steroid-refractory patients. Clin Gastroenterol Hepatol 2015;13:452–8. [PubMed: 25086190]

37. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, Spechler SJ, Attwood SE, Straumann A, Aceves SS, Alexander JA, Atkins D, Arva NC, Blanchard C, Bonis PA, Book WM, Capocelli KE, Chehade M, Cheng E, Collins MH, Davis CM, Dias JA, Di Lorenzo C, Dohil R, Dupont C, Falk GW, Ferreira CT, Fox A, Gonsalves NP, Gupta SK, Katzka DA, Kinoshita Y, Menard-Katcher C, Kodroff E, Metz DC, Miehlke S, Muir AB, Mukkada VA, Murch S, Nurko S, Ohtsuka Y, Orel R, Papadopoulou A, Peterson KA, Philpott H, Putnam PE, Richter JE, Rosen R, Rothenberg ME, Schoepfer A, Scott MM, Shah N, Sheikh J, Souza RF, Strobel MJ, Talley NJ, Vaezi MF, Vandenplas Y, Vieira MC, Walker MM, Wechsler JB, Wershil BK, Wen T, Yang GY, Hirano I, Bredenoord AJ. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. Gastroenterology 2018;155:1022–1033.e10. [PubMed: 30009819]
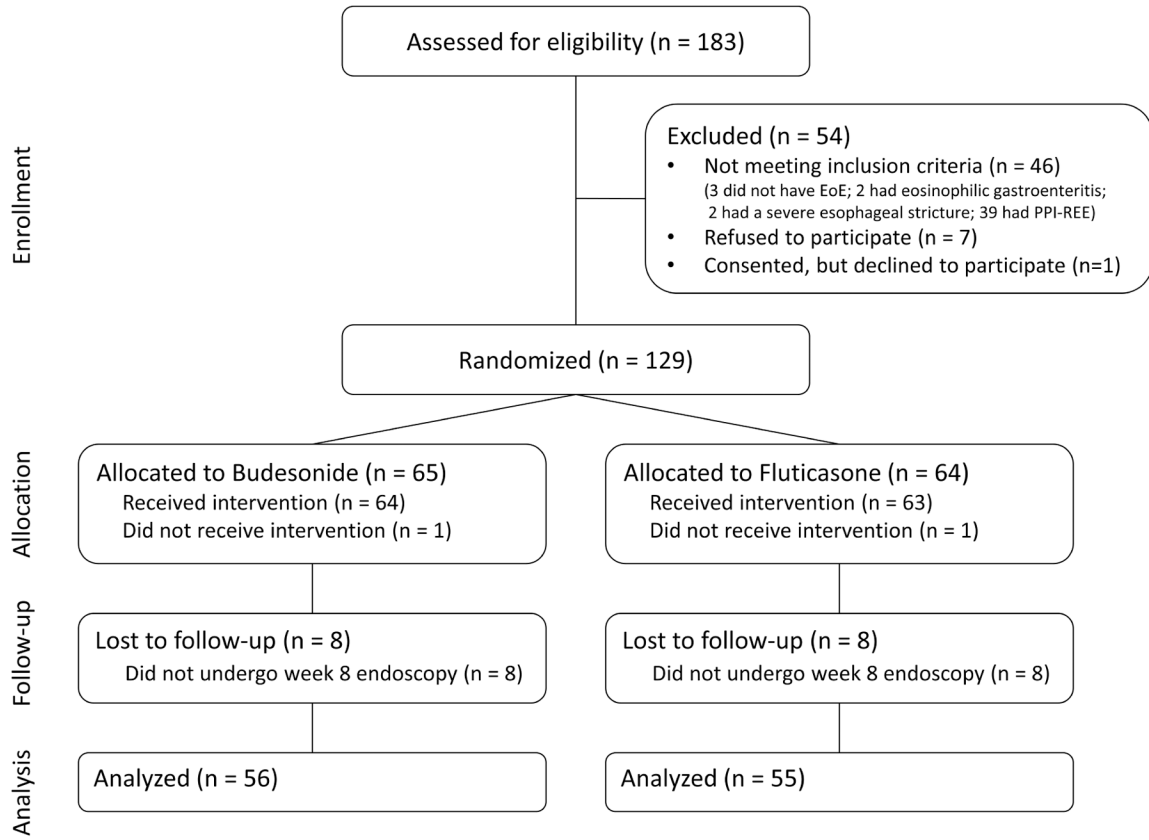
Figure 1.
CONSORT diagram, with subject flow through the study. The majority of subjects who did not meet the eligibility requirements had proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE; n=46). Of the 16 subjects who were lost to follow-up after randomization and receiving study intervention, 6 did not tolerate the medications due to taste, 8 either no longer wanted to participate due to study logistics or could not be reached, 1 had an adverse event of a food bolus impaction necessitating an ER visit and study withdrawal, and 1 had an environmental allergic reaction requiring a systemic corticosteroids that necessitated study withdrawal.
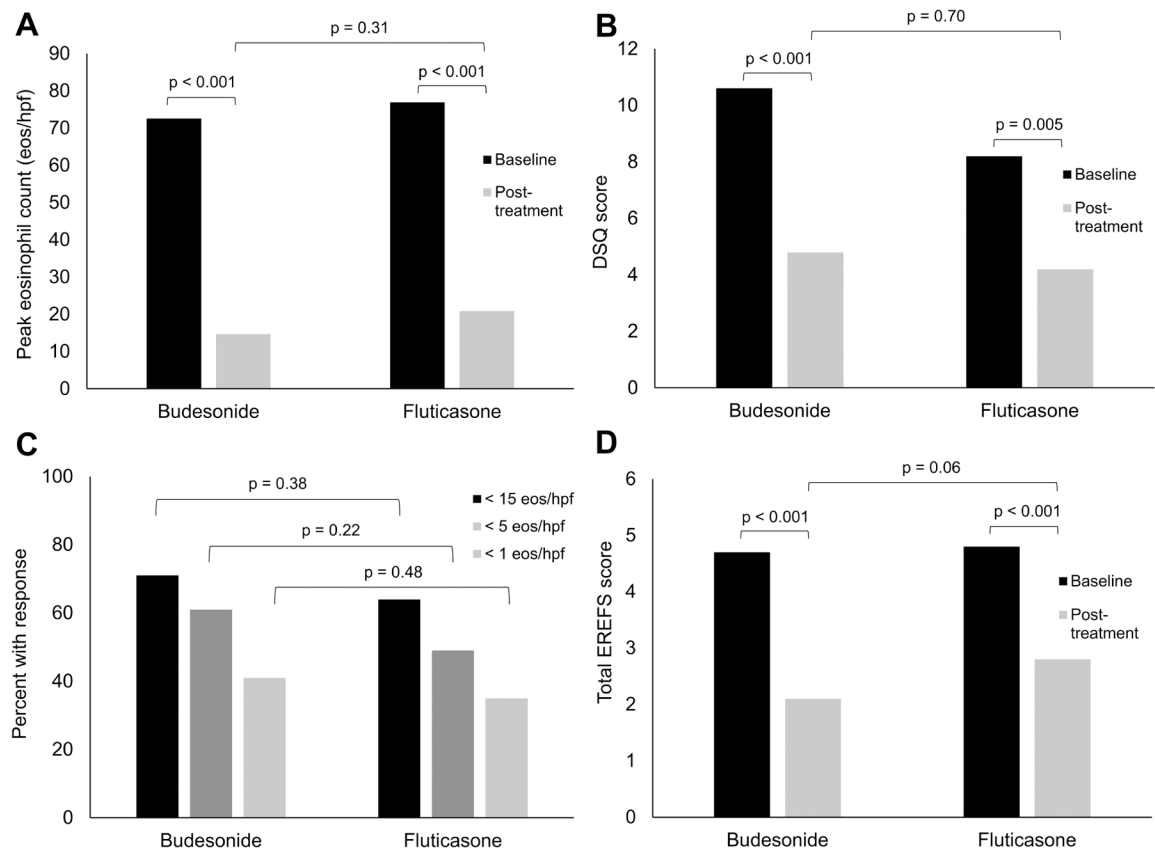
Figure 2.
Study outcome measures. **(A)** Primary outcome of peak eosinophil count. **(B)** Co-primary outcome of the Dysphagia Symptom Questionnaire (DSQ) score. **(C)** Secondary outcome of histologic response thresholds of <15, <5, and <1 eos/hpf. **(D)** Secondary outcome of the EoE Endoscopic Reference Score (EREFS).

Table 1:

Baseline characteristics of all randomized study subjects

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

[*] Patient self-report; could include an overt reaction or sensitization

Table 2:

Key primary and secondary histologic, symptom, and endoscopic outcomes

	Budesonide	Fluticasone	p
Histologic outcomes	n = 56	n = 55	
Peak eosinophil count (eos/hpf ± SD)			
Baseline	72.6 ± 45.6	76.9 ± 62.3	0.67
Post-treatment *	14.7 ± 29.0	20.9 ± 34.3	0.31
p value (paired pre/post treatment)	< 0.001	< 0.001	
Absolute change in count	−57.9 ± 55.9	−56.1 ± 55.6	0.57
Percentage change in count	−70.8 ± 64.1	−71.7 ± 44.1	0.93
Histologic response thresholds (n, %)			
<15 eos/hpf	40 (71)	35 (64)	0.38
<5 eos/hpf	34 (61)	27 (49)	0.22
<1 eos/hpf	23 (41)	19 (35)	0.48
Symptom outcomes			
DSQ score (mean ± SD)	n = 46	n = 38	
Baseline	10.6 ± 9.3	8.2 ± 9.9	0.26
Post-treatment *	4.8 ± 7.3	4.2 ± 7.5	0.70
p value (paired pre/post treatment)	< 0.001	0.005	
Change in DSQ	−5.8 ± 9.6	−4.0 ± 8.3	0.37
EEsAI score (mean ± SD)	N=32	N=38	
Baseline	36.5 ± 23.3	35.9 ± 20.4	0.91
Post-treatment	22.1 ± 18.9	28.0 ± 20.4	0.22
p value (paired pre/post treatment)	< 0.001	0.005	
Change in EEsAI	−14.4 ± 15.7	−7.9 ± 16.2	0.10
EEsAI in remission (n, %)			
Baseline	11 (29)	11 (26)	0.73
Post-treatment	17 (43)	18 (39)	0.75
Endoscopic outcomes	n = 56	n = 55	
Total EREFS score (mean ± SD)			
Baseline	4.7 ± 1.8	4.8 ± 2.0	0.89
Post-treatment	2.1 ± 1.7	2.8 ± 2.2	0.06
p value (paired pre/post treatment)	< 0.001	< 0.001	
Change in EREFS	−2.6 ± 1.8	−1.9 ± 2.0	0.07

*
Co-primary outcomes

†
Defined as a score <20

Table 3:

Predictors of histologic treatment response

	Non-responders (≥15 eos/hpf) (n = 36)	Responders (<15 eos/hpf) (n = 75)	p
Age (mean years ± SD; range)	35.2 ± 14.1	40.8 ± 15.5	0.07
Male (n, %)	25 (69)	49 (65)	0.67
White (n, %)	33 (92)	74 (99)	0.06
BMI (mean kg/m^2 ± SD)	28.8 ± 7.1	26.2 ± 6.1	0.05
Length of dysphagia (mean years ± SD)	10.0 ± 1.7	11.0 ± 9.8	0.63
DSQ score (mean ± SD)	10.4 ± 11.8	8.8 ± 9.3	0.48
EEsAI score (mean ± SD)	40.1 ± 27.0	33.3 ± 20.1	0.18
Any atopic condition (n, %)	26 (72)	56 (75)	0.78
Asthma	13 (36)	18 (24)	0.18
Eczema	3 (8)	18 (24)	0.05
Seasonal allergies/allergic rhinitis	22 (64)	45 (60)	0.69
Food allergies [*]	16 (44)	31 (41)	0.76
Endoscopic features			
Total EREFS score (mean ± SD)	5.30 ± 1.62	4.47 ± 1.93	0.03
Inflammatory EREFS score (mean ± SD)	3.33 ± 0.93	2.61 ± 1.25	0.003
Fibrotic EREFS score (mean ± SD)	1.97 ± 1.06	1.85 ± 1.02	0.57
EREFS components			
Exudates (mean ± SD)	1.22 ± 0.64	0.76 ± 0.61	< 0.001
Rings (mean ± SD)	1.44 ± 0.81	1.21 ± 0.83	0.17
Edema (mean ± SD)	0.94 ± 0.23	0.75 ± 0.44	0.01
Furrows (mean ± SD)	1.17 ± 0.38	1.11 ± 0.56	0.56
Stricture (mean ± SD) [†]	0.53 ± 0.51	0.64 ± 0.48	0.26
Stricture size (mm ± SD)	11.6 ± 2.3	13.0 ± 3.0	0.07
Narrowing (n, %) [†]	17 (47)	12 (16)	< 0.001
Dilation required at baseline exam (n, %)	19 (53)	41 (55)	0.85
History of prior esophageal dilation (n, %)	20 (56)	39 (52)	0.73
Pull sign positive (n, %)	21 (64)	32 (49)	0.18
Peak overall eosinophil count (eos/hpf ± SD)	90.5 ± 68.4	67.2 ± 44.7	0.03
Proximal peak	58.3 ± 56.7	33.2 ± 39.2	0.008
Distal peak	75.8 ± 65.4	59.7 ± 43.6	0.13
Degranulation (n, %)	28 (78)	50 (67)	0.23
Microabscess (n, %)	32 (89)	55 (73)	0.06
Spongiosis (n, %)	34 (94)	65 (87)	0.22
Lamina propria fibrosis (n, %)	28 (88)	39 (80)	0.36

[*] Patient self-report; could include an overt reaction or sensitization

[†] Stricture is defined as a focal impingement in the esophageal lumen; narrowing is defined as a more diffuse decrease in esophageal caliber

Table 4:

Adverse events

	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	10 (15)	15 (23)
Serious adverse event	0 (0)	1 (2)