

Comparison of Esomeprazole to Aerosolized, Swallowed Fluticasone for Eosinophilic Esophagitis

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Received: 28 January 2009 / Accepted: 19 May 2009
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Abstract

Background Both gastroesophageal reflux disease and allergy/atopy have been implicated in the pathogenesis of eosinophilic esophagitis (EoE). There are no prospective studies comparing treatment of EoE with acid suppression versus topical corticosteroids.

Objective To determine the outcome of adult eosinophilic esophagitis patients treated with esomeprazole versus topical fluticasone.

Design Prospective randomized controlled trial.

Setting Academic medical center.

Participants Adults (18–80) diagnosed with EoE by symptoms of dysphagia and esophageal biopsies with ≥ 15 eosinophils/hpf.

Interventions Subjects were randomized to esomeprazole (40 mg by mouth every morning) or aerosolized, swallowed fluticasone (440 mcg by mouth twice a day) for 8 weeks.

Main Outcome Measurements Improvement in dysphagia (8-point scale), esophageal eosinophil infiltration before and after treatment, prevalence of GERD measured by validated questionnaire and baseline pH study.

Results About 56% (14/25) had acid reflux by pH study. There was no difference between treatment groups in improvement in dysphagia scores [3/12 (25%) of the esomeprazole group versus 6/12 (50%) in the fluticasone group, $P = 0.40$]. Eosinophil infiltration decreased with

treatment in both groups, and there was no difference in the amount of decrease between groups ($P = 0.70$).

Limitations Small sample size, unexpectedly high drop-out rate.

Conclusions Gastroesophageal reflux disease is common in adult eosinophilic esophagitis patients. Dysphagia improves and esophageal eosinophil infiltration decreases with either treatment. There was no difference in degree of improvement in dysphagia or eosinophil infiltration in patients treated with either topical fluticasone or oral esomeprazole. GERD may be important in the pathogenesis of adult EoE.

Keywords Eosinophilic esophagitis · Dysphagia · Gastroesophageal reflux disease

Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized condition characterized by dysphagia, food impaction and/or chest pain in predominantly young to middle-aged males [1, 2]. The etiology of EoE is not clear, and hypotheses are conflicting. Eosinophilic esophagitis in patients may develop as an atopic response to specific stimuli, often presenting with a Th2-type response. A personal and family history of allergic diseases (food allergies, atopic dermatitis, asthma, allergic rhinitis or conjunctivitis) has been noted in 62–85% of patients with EoE [3, 4]. Elevated IgE levels have been demonstrated in up to 70% of patients [5–7]. Current treatment of EoE is directed at decreasing esophageal allergic response. Oral and topical corticosteroids, cromolyn sodium, monoleukast and elemental/elimination diets have all been used for treatment of EoE in pediatric populations [6, 8–10]. Topical steroids are

Funding support was provided in part by an ASGE Research grant.

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most often given as aerosolized fluticasone sprayed into the mouth and then swallowed [11, 12]. These studies were open label without control or comparison groups, and most were retrospective, but all reported topical corticosteroid therapy to be very effective in patients diagnosed with EoE [9, 11–16]. In the only randomized, controlled trial using steroids, Konikoff et al. [14] found oral topical fluticasone to be superior to placebo in achieving histologic resolution, but overall resolution was only 50%. In addition, in a previous smaller case series fluticasone was not effective [13]. Successful treatment of EoE has also been reported using acid suppression. In a small retrospective study, all 19 patients with ringed esophagus had response to proton pump inhibitor (PPI) combined with dilation [17]. Ngo et al. [18] reported three patients with marked esophageal eosinophilia who responded dramatically to PPI therapy.

Despite data from different studies suggesting the efficacy of suppression in the treatment of EoE, no trials have directly compared the use of a PPI to topical corticosteroids in the treatment of EoE. We hypothesized that fluticasone therapy would demonstrate increased efficacy in the treatment of EoE as compared to acid suppression with esomeprazole.

Materials and Methods

IRB approval was obtained at the University of Utah and registered at www.clinicaltrials.gov, trial no. NCT00123656. All procedures were performed and data collected at the University of Utah Health Sciences Center. Patients with EoE ages 18–80 years old who could undergo pH and manometry testing were included. EoE was defined as ≥ 15 eosinophils averaged over five high power fields on esophageal biopsy in subjects with symptoms of dysphagia, food impaction or chest pain. Patients were excluded if they had to be dilated on the first exam (due to inability to pass an upper endoscope), had a history of a contraindication or intolerance of either fluticasone or PPIs, were pregnant or incarcerated, had a history of prior upper gastrointestinal surgery, had other potential alternative mechanisms for dysphagia demonstrated at endoscopy, current use of PPIs or glucocorticoids, or symptoms of food impaction to food bolus size < 1 cm. Potential subjects underwent initial endoscopy with four quadrant biopsies in the proximal and distal esophagus. If the subjects qualified histologically, they underwent esophageal manometry and pH testing (antimony pH slimline probe or Bravo pH probe, both Medtronic, Shoreview, MN) before randomization to treatment arms. pH results were considered positive if the patients demonstrated $> 4.2\%$ time distal acid exposure or $> 0.9\%$ time proximal acid exposure of pH < 4 [16, 17]. Subjects completed a dysphagia scale [19] and the validated reflux disease questionnaire (RDQ) [20] prior to

randomization to medication and at the end of the study. The dysphagia scale ranged from 0 to 7. A score of 0 was equal to no dysphagia; 1 = solid food dysphagia once in 3–12 months; 2 = solid food dysphagia once in 1–3 months; 3 = solid food dysphagia once every 2–4 weeks; 4 = solid food dysphagia once every 1–2 weeks; 5 = solid food dysphagia once every 1–7 days; 6 = solid food dysphagia with every meal; 7 = dysphagia to solid and liquid food.

Randomization and Treatment

Subjects were randomized to either swallowed aerosolized fluticasone (440 mcg b.i.d.) or esomeprazole 40 mg a day for 8 weeks. Subjects were instructed not to eat or drink for 30 min after fluticasone administration. Subject medication compliance was verified verbally at the end of study visit. Randomization was achieved via a computer-assisted program with a 1:1 randomization scheme. At the end of 8 weeks, dysphagia score and RDQ were repeated. Upper endoscopy with four quadrant proximal and distal biopsies and histologic evaluation for eosinophils was also repeated at 8 weeks. Neither the participants nor the investigators were blinded to treatment; however, the pathologist was blinded. The randomization sequence was concealed until assignment to the investigators. The research staff generated the random sequence and assigned the participants to treatment group after the investigator who performed the endoscopy enrolled the participant.

Histological Analysis

Esophageal biopsies were fixed in 10% neutral buffered formalin and processed into paraffin by the rapid microwave-assisted method routinely used in our laboratory [21]. Sections were cut at 4 μm and stained by routine hematoxylin and eosin. A single pathologist (LLE) evaluated each histologic slide blindly. Each high power field (HPF) was 400 $\times$ magnification (i.e., 40 $\times$ objective lens and 10 $\times$ ocular lens, Olympus BX51 microscope, 0.53 mm² per field measured by ocular micrometer). A low power impression of the area of highest density of eosinophils was made, and counting of eosinophils was started in this area. Only intact eosinophil nuclei within esophageal squamous mucosa were counted. Five consecutive high power fields were counted. The average count of eosinophils per high power field was calculated from these five fields.

Endpoints

We hypothesized that we would see superiority in the fluticasone arm based on prior data. We anticipated an 80% response rate (defined as a decrease in dysphagia score of

at least two points) in the fluticasone arm as compared to a 33% response rate in the esomeprazole arm as the primary endpoint. Secondary endpoints included change in eosinophilic infiltration in esophageal biopsies. We arbitrarily defined partial resolution as ≤ 15 eos/HPF and complete resolution as ≤ 5 eos/HPF.

Comparisons before and after therapy were made within and between groups for change in dysphagia score and eosinophil infiltration. Pathologist interpretation of the biopsy specimens was blinded to the subjects' treatment arms. Sample size (with an alpha error of 0.05, beta error of 0.20 and dropout of 10%) was calculated to equal 30 subjects (15 in each arm) based on the primary endpoint. Eosinophil infiltration and dysphagia scores were compared between groups via the Wilcoxon rank sum test and within groups via the Wilcoxon signed rank test. Fisher's exact analysis was utilized to evaluate the partial or complete resolution of EoE between the two treatment arms. A P -value of <0.05 was considered to be significant. All tests were analyzed as two-tailed unless otherwise noted. Spearman's coefficient was used for correlation of dysphagia scores with intensity of eosinophilic infiltration.

Results

Thirty patients with EoE were enrolled from January 2005 until October 2006 and followed until December 2006. Four subjects dropped out prior to completion of the study (three esomeprazole, one fluticasone). None of these patients underwent pH testing. Reasons for drop-out were

unwillingness to perform the second EGD in three patients. One patient was withdrawn by the IRB for an interpretation of "inadequate pathology." All dropouts occurred prior to completion of the second dysphagia questionnaire. Two patients who completed the second EGD did not complete the second dysphagia questionnaire.

Baseline demographics did not differ significantly between the groups (Table 1). For the total group, mean age was 37 years old (18–79). Overall, 20/30 were male (77%). The average age of subjects in the esomeprazole group was 38.8 years (26–79) and 34.6 (18–58) years in the fluticasone group. In the esomeprazole group, 12/15 (80%) of subjects were male as compared to 11/15 (73%) in the fluticasone group ($P = 1.0$).

Average dysphagia score at baseline was 3.5 ± 2.0 (range 1–6) in the esomeprazole group versus 3.7 ± 2.0 (range 1–7) in the fluticasone group ($P = 0.75$). Baseline eosinophil counts (mean eosinophil count of five high power fields in area of highest density) were not significantly different ($P = 0.32$) between the groups with 45.8 ± 30.7 eosinophils in the esomeprazole group versus 62.1 ± 53.2 in the fluticasone group. The mean of the eosinophil infiltration in the highest single high power field per patient is reported as well (Table 1). Overall, 14/25 (56%) of subjects demonstrated abnormal 24 h pH, while 17/29 (58%) were diagnosed with gastroesophageal reflux disease (GERD) according to the RDQ. One subject's RDQ and one subject's pH data were not available for analysis. There was no significant difference between the groups in the proportion with abnormal RDQ or pH monitoring at baseline. There were no significant adverse events in either treatment group.

Table 1 Patient demographics

	Esomeprazole ($n = 15$)	Fluticasone ($n = 15$)	Total
Age, mean (range)	38.8 years (26–79)	34.6 years (18–58)	37 years (18–79)
Gender (M/F)%	12/M 3/F (80%)	11/M 4/F (73%)	23/M 7/F
Eosinophil infiltration			
Pre-tx mean $\pm$ SD (range; mean of 5 hpfs per pt)	45.8 ± 30.7 (15–131.2)	62.1 ± 53.2 (15–239)	58.0 ± 46.0
Pre-tx mean max $\pm$ SD (range; mean of highest single hpf per pt)	69.8 ± 37.4 (15–168)	92 ± 65.4 (19–292)	80.4 ± 54.4 (15–292)
Post-tx mean $\pm$ SD (range; mean of 5 hpfs per pt)	22.1 ± 20.6 (0–56.8)	30.1 ± 25.3 (0–84.2)	26.3 ± 23.1
Post-tx mean max $\pm$ SD (range; mean of highest single hpf per pt)	37.2 ± 28.6 (0–79)	48.1 ± 42 (0–153)	42.8 ± 35.9 (0–153)
Dysphagia			
Pre-tx dysphagia score	3.5 ± 2.0	3.7 ± 2.0	
Post-tx dysphagia score	2.3 ± 2.0	1.7 ± 1.6	
Abnormal 24-h pH, n (%)	7/12 (58%)	7/13 (53%)	14/25 (56%)
Pre-treatment reflux (RDQ score)	10/15 (67%)	7/14 (50%)	
Endoscopic findings			
Rings, n (%)	15/15 (100)	14/15 (93)	
Furrows, n (%)	1/15 (0.7)	1/15 (0.7)	
Abscesses, n (%)	2/15 (13)	3/15 (20)	

Analysis

At the end of treatment, there was no significant difference in the primary endpoint of improvement in dysphagia scores by at least two points between the groups [3/12 (25%) of the esomeprazole group versus 6/12 (50%) in the fluticasone group, $P = 0.40$]. When patients with baseline dysphagia scores of 1 and 2 were removed from the analysis, there was still no significant difference ($P = 0.6$). There was also no significant difference between the esomeprazole and fluticasone arms regarding improvement in average dysphagia scores (Figs. 1, 2) or eosinophil infiltration ($P = 0.61$ and 0.70 , respectively, $P = 0.19$; Figs. 3, 4). The mean eosinophil infiltration did decrease significantly with treatment in the esomeprazole group (45.8 ± 30.7 pre-treatment to 22.1 ± 20.6 post treatment, $P = 0.02$) and nearly significant in the fluticasone group

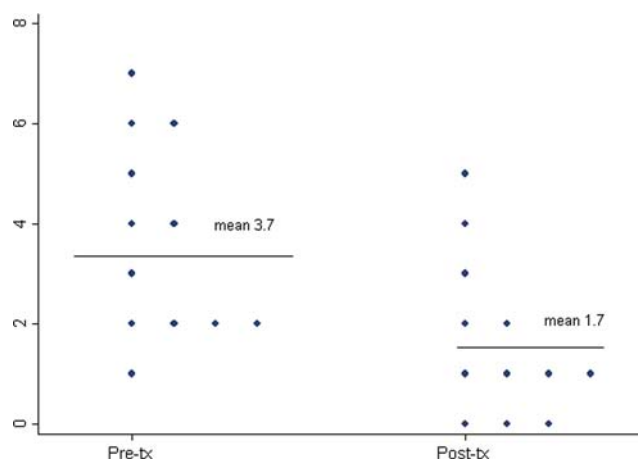


Fig. 1 Dot plot graph of dysphagia scores pre- and post-treatment with fluticasone

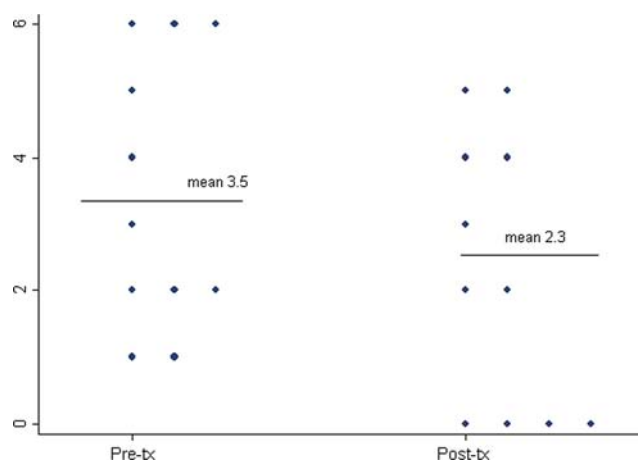


Fig. 2 Dot plot graph of dysphagia scores pre- and post-treatment with esomeprazole

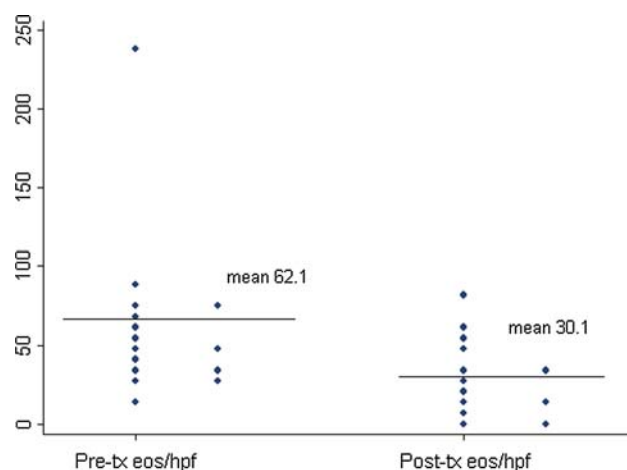


Fig. 3 Dot plot graph of eosinophil infiltration pre- and post-treatment with fluticasone

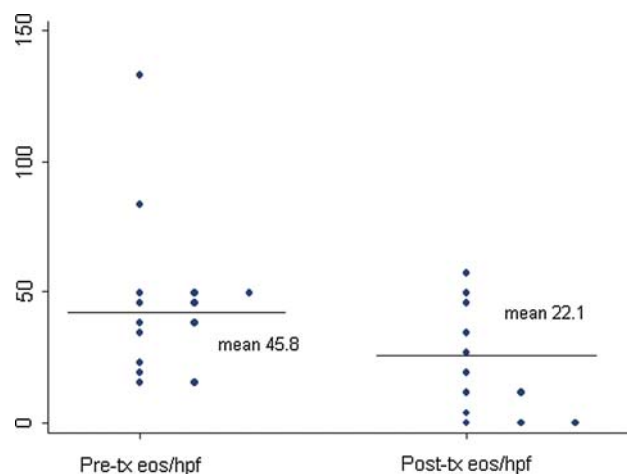


Fig. 4 Dot plot graph of eosinophil infiltration pre- and post-treatment with esomeprazole

(62.1 ± 53.2 pre-treatment to 30.1 ± 25.3 post-treatment, $P = 0.07$).

A subgroup analysis of only those with abnormal baseline pH study did not demonstrate a significant difference in improvement of dysphagia scores by at least two points in both treatment groups (4/7 in the fluticasone group vs. 1/7 in the esomeprazole group; $P = 0.3$). The mean eosinophil change was -13.2 (range -33.8 to $+11.8$) in the fluticasone group and -32.9 (range -74.4 to $+4.4$) in the esomeprazole group. The decrease in eosinophil infiltration between the treatment groups was also not significant ($P = 0.12$).

In an exploratory analysis of partial resolution of EoE as defined by post-treatment biopsies demonstrating ≤ 15 eos/HPF, the groups displayed similar efficacy with no apparent superior treatment [esomeprazole partial resolution 6/12 (50%) vs. fluticasone partial resolution 4/13 (31%), per protocol analysis $P = 0.28$]. Additionally, there was no

significant difference in complete resolution between groups, defined by post-treatment biopsies demonstrating ≤ 5 eos/HPF (2/13 or 15% complete resolution in the fluticasone group versus 4/12 or 33% complete resolution in the esomeprazole group, per protocol analysis $P = 0.38$). Intention to treat (ITT) analysis also did not demonstrate a difference between the groups for either partial or complete resolution. We also found no correlation between dysphagia scores and intensity of eosinophilic infiltrate or improvement within either group (fluticasone, $P = 0.83$; esomeprazole, $P = 0.76$).

Discussion

Our study is the first prospective, randomized, controlled trial comparing swallowed aerosolized steroids to acid suppression in the adult population with ringed esophagus with eosinophilic infiltration. A recent publication of a randomized, controlled, blinded trial of fluticasone versus placebo in pediatric patients demonstrated the superiority of fluticasone to placebo in inducing histologic remission [14]. There are no prospective studies of the efficacy of acid suppression with PPIs in EoE. In our comparative trial, neither treatment appeared superior in its efficacy, with both treatments resulting in approximately 50% or less improvement of dysphagia or partial histologic resolution and even poorer results for complete histologic resolution. Both treatments decreased the eosinophilic infiltration in the esophagus, though only treatment with esomeprazole reached statistical significance. The results of treatment with fluticasone are very similar to those of Konikoff et al. [14], with only one-third to one-half of our patients improving with topical steroid treatment and significantly less than that reported in previous uncontrolled studies.

These findings may be due to a variety of reasons. We used a dysphagia score to define our primary endpoint. However, dysphagia is a subjective complaint, and the patients were not blinded to their treatment. At the time of our study there were no validated dysphagia measures; therefore, we used one we had previously used in other treatment studies of dysphagic patients [22]. In this study the dysphagia scores did not reflect the degree of eosinophil infiltration or correlate with improvement in eosinophil infiltration. Thus, dysphagia assessment may not be the optimal outcome by which to assess patients' outcomes. However, further support for the lack of difference in dysphagia scores between treatment groups is the lack of a significant difference between treatment groups in our secondary endpoints (average eosinophil counts, partial and complete resolution of eosinophilic infiltration).

We chose the histologic definition of ≥ 15 eos/HPF averaged over 5 HPF as our diagnostic cutoff for EoE

based on our own experience and extensive review of the EoE literature. Previous published data suggests that >10 eos/HPF on biopsy of the esophagus is extremely uncommon in patients with GERD alone [4, 23, 24]. Additionally, a recent consensus conference histologically defined EoE as >15 – 20 eosinophils in *any* HPF [1]. We chose to increase our specificity for the disease based on a more stringent criteria of an *average* of ≥ 15 eos/HPF over 5 HPFs. Thus, our secondary endpoint of "resolution" (as defined by the average of <5 eos/HPFs over 5 HPFs) may have been more stringent in its criteria.

Finally, our numbers studied were small, subjecting us to the possibility of a type II error. We did expect a larger difference in efficacy to be seen between the groups, and this was reflected in our sample size calculation. There was a numerical, but not statistical superiority of the fluticasone over esomeprazole-treated patients. However, the lack of a true significant difference between the two treatments is supported by the lack of difference in histological endpoints in our study. Thus, if there is a difference in efficacy between the two therapies, it is likely not as great as suggested by the previous uncontrolled studies in the literature.

A recent consensus review stated that acid reflux is independent of EoE, and it should not be diagnosed until GERD is ruled out by pH monitoring or a trial of acid suppression, yet our results suggest otherwise. EoE is thought to be primarily an atopic disease. Prior investigators have demonstrated increases in immunoregulatory factors associated with allergic response, including increases in IL-4, IL-5, TNF- α , lymphocytes, mast cells and eosinophil major basic protein (MBP), all suggesting an allergic pathogenesis of EoE [25]. EoE appears to be a TH-2, IL-5, mast cell, IgE-associated disease process strikingly similar to the immune mechanisms involved in asthma [25]. The rising incidence of EoE may be related to the worldwide allergy and asthma epidemic.

There may be a substantial difference in the pathophysiology between adult and pediatric populations, and our study included only adult patients. pH monitoring in children with EoE suggests that the pediatric population does not suffer from an abnormally increased frequency of GERD [26, 27]. However, the adult population with EoE appears to suffer from an increased prevalence of abnormal esophageal reflux [11, 28, 29]. Remedios et al. [11] found 38% of their patients had abnormal acid reflux. Our prevalence of abnormal pH (56%) is higher than reported in other studies and may be due to the fact that the majority of our patients underwent BRAVO catheter analysis allowing for 48 h of data to be collected, increasing our sensitivity for finding abnormal acid reflux. Morrow et al. [17] found that many of the histologic features of eosinophilic esophagitis are found in patients with GERD, only to a more severe degree (basal cell hyperplasia, papillomatosis,

eosinophils). This has led some to suggest that EoE and GERD may be pathophysiologically interrelated [30]. Due to our high prevalence of acid reflux, treatment with acid suppression may have allowed for an enhanced response in possible “esophageal reflux” patients. However, this does not explain why such patients had such marked eosinophilic infiltration, significantly above that typically thought to be related to acid reflux. In addition, we found no difference in our results when we categorized the groups via +GERD and –GERD based on our pH results, although the number of subjects in each group was very small. As stated previously, both treatments reduced esophageal eosinophilia, with the decrease in the esomeprazole group being statistically significant. However, the decrease in the fluticasone group almost reached statistical significance, and there was no difference in the degree of reduction when comparing between groups rather than to baseline. Our findings suggest that acid reflux may contribute substantially to the development of EoE, and its role in the disease in adults should not be minimized.

Indeed, GERD and EoE may actually be synergistic in the adult population. In an eloquent review, *Spechler* postulated why acid reflux appears to be more prevalent in EoE. It may be that acid reflux contributes to the disease, but is not the sole cause of it. Reflux may contribute to the pathogenesis of EoE by causing increased intracellular spaces by which antigens may come into contact with the subepithelium [30–32]. Increased allergen exposure would lead to increased eosinophil infiltration. This could lead to increased acid reflux due to eosinophilic degranulation and motility disturbances caused either directly (via MBP) or indirectly (fibrosis) by eosinophils perpetuating the cycle. Others have suggested that treatment with high dose acid suppression may allow for resolution of dilated intracellular spaces (DIS) and defense against antigenic stimulus [31].

The potential role of aeroallergens in EoE with variability in allergen exposure may have affected our results. Recent literature suggests a relationship between aeroallergens and EoE [33]. If there is chronological and/or seasonal variation of EoE due to aeroallergen exposure, it is possible that some patients underwent biopsies during fluctuations of their allergies, and any improvement may be related to this variation in their underlying allergic disease not related to the medications given. Unfortunately, we did not collect information on the allergic profile of our patients. However, this should have affected both treatment arms, and patients were enrolled and randomly treated over a ~2 year period.

Finally, fluticasone’s method of action is thought to be related to direct mucosal contact. However, no studies have investigated the distribution of swallowed aerosolized fluticasone in the esophagus. Thus, fluticasone could

potentially fail, not due to its inability to control inflammation, but due to its lack of adequate delivery. Recent data by Aceves [34] demonstrated improvement in patients refractory to swallowed aerosolized fluticasone with a suspension of budesonide, suggesting that different forms of administration of steroids may be useful in the treatment of EoE.

In summary, our randomized prospective trial of swallowed fluticasone versus esomeprazole failed to reveal the superiority of either drug in the treatment of EoE by any of our endpoints. This is the first study prospectively comparing acid suppression to fluticasone in the treatment of EoE using pre-defined dysphagia measurement, assessment of abnormal acid reflux by pH testing and stringent histologic criteria. It has been suggested in a consensus definition of EoE that patients must fail to eradicate their eosinophils on acid suppression before the diagnosis of EoE can be made. However, in adults a high percentage of such patients with dense esophageal infiltration will have co-existent GERD. In addition, our data suggests that treatment with either PPI or topical corticosteroids will result in similar improvement in symptoms and eosinophilic infiltration regardless of underlying GERD. Further studies are warranted to carefully delineate the contribution of acid reflux in adult EoE patients and determine whether therapy should include acid suppression, topical steroids or perhaps both.

References

1. Furuta G, Licouras C, Collins M, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133:1342–1363. doi:[10.1053/j.gastro.2007.08.017](https://doi.org/10.1053/j.gastro.2007.08.017).
2. Liacouras C. Eosinophilic esophagitis in children and adults. *J Pediatr Gastroenterol Nutr*. 2003;37(Suppl 1):S23–S28.
3. Orebaugh H, Peterson K, Kuwada S, Fang J. Ringed esophagus is associated with atopy not GERD. *Gastroenterology*. 2003;124:A235. doi:[10.1016/S0016-5085\(03\)81181-2](https://doi.org/10.1016/S0016-5085(03)81181-2).
4. Fox V, Nurko S, Furuta G. Eosinophilic esophagitis: it’s not just kid’s stuff. *Gastrointest Endosc*. 2002;56:260–270. doi:[10.1016/S0016-5107\(02\)70188-0](https://doi.org/10.1016/S0016-5107(02)70188-0).
5. Straumann A, Spichtin H, Grize L, Bucher K, Beglinger C, Simon H. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003;125:1660–1669.
6. Spergel J, Andrews T, Brown-Whitehorn T, Beausoleil J, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol*. 2005;95:336–343.
7. Sant’Anna A, Rolland S, Fournet J, Yazbeck S, Drouin E. Eosinophilic esophagitis in children: symptoms, histology and pH probe results. *J Pediatr Gastroenterol Nutr*. 2004;39:373–377. doi:[10.1097/00005176-200410000-00013](https://doi.org/10.1097/00005176-200410000-00013).
8. Orenstein S, Shalaby T, Lorenzo C, Putnam P, Sigurdsson L, Kocochis S. The spectrum of pediatric eosinophilic esophagitis

- beyond infancy: a clinical series of 30 patients. *Am J Gastroenterol.* 2000;95(6):1422–1430.
9. Teitelbaum J, Fox V, Twarog F, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology.* 2002;122:1216–1225. doi:[10.1053/gast.2002.32998](https://doi.org/10.1053/gast.2002.32998).
 10. Attwood S, Lewis C, Bronder C, Morris C, Armstrong G, Whittam J. Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut.* 2003;52(8):1228–1229.
 11. Remedios M, Campbell C, Jones D, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc.* 2006;63:3–12. doi:[10.1016/j.gie.2005.07.049](https://doi.org/10.1016/j.gie.2005.07.049).
 12. Lucendo A, Pascual Turrion JM, Navarro M, et al. Endoscopic, biptic, and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. *Endoscopy.* 2007;39:765–771. doi:[10.1055/s-2007-966738](https://doi.org/10.1055/s-2007-966738).
 13. Langdon D. Fluticasone in eosinophilic corrugated ringed esophagus. *Am J Gastroenterol.* 2001;96(3):926–927.
 14. Konikoff M, Noel R, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology.* 2006;131:1381–1391. doi:[10.1053/j.gastro.2006.08.033](https://doi.org/10.1053/j.gastro.2006.08.033).
 15. Arora A, Perrault J, Smyrk T. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc.* 2003;78:830–835. doi:[10.4065/78.7.830](https://doi.org/10.4065/78.7.830).
 16. Faubion W, Perrault J, Burgart L, Zein N, Clawson M, Freese D. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr.* 1998;27(1):118–119.
 17. Morrow J, Vargo J, Goldblum J, Richter J. The ringed esophagus: histological features of GERD. *Am J Gastroenterol.* 2001;96:984–989. doi:[10.1111/j.1572-0241.2001.03682.x](https://doi.org/10.1111/j.1572-0241.2001.03682.x).
 18. Ngo P, Furuta G, Antonioli D, Fox V. Eosinophils in the esophagus—Peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol.* 2006;101:1666–1670. doi:[10.1111/j.1572-0241.2006.00562.x](https://doi.org/10.1111/j.1572-0241.2006.00562.x).
 19. DiSario J, Pedersen P, Bichis-Canoutas C, Alder S, Fang J. Incision of recurrent distal esophageal (Schatzki) ring after dilation. *Gastrointest Endosc.* 2002;56:244–248. doi:[10.1016/S0016-5107\(02\)70185-5](https://doi.org/10.1016/S0016-5107(02)70185-5).
 20. Aanan M, Numens M, Wusten B, Smout A. Diagnostic value of the reflux disease questionnaire in general practice. *Digestion.* 2006; 74:162–168.
 21. Emerson L, Tripp S, Baird B, Layfield L, Rohr L. A comparison of immunohistochemical stain quality in conventional and rapid microwave processed tissues. *Am J Clin Pathol.* 2006;125: 176–183.
 22. Wills J, Hilden K, DiSario J, Fang J. A randomized, prospective trial of electrosurgical incision followed by rabeprazole versus bougie dilation followed by rabeprazole of symptomatic esophageal (Schatzki's) rings. *Gastrointest Endosc.* 2008;67:808–813. doi:[10.1016/j.gie.2007.10.062](https://doi.org/10.1016/j.gie.2007.10.062).
 23. Brown L, Goldman H, Antonioli D. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. *Am J Surg Pathol.* 1984;8:899–905. doi:[10.1097/0000478-198412000-00002](https://doi.org/10.1097/0000478-198412000-00002).
 24. Tummala V, Barwick K, Sontag S, Vlahsevic R, McCallum R. The significance of intraepithelial eosinophils in the histologic diagnosis of gastroesophageal reflux. *Am J Clin Pathol.* 1987;87: 43–48.
 25. Gupta S, Fitzgerald J, Kondratyuk T, HogenEsch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2006;42:22–26. doi:[10.1097/01.mpg.0000188740.38757.d2](https://doi.org/10.1097/01.mpg.0000188740.38757.d2).
 26. Steiner S, Gupta S, Croffie J, Fitzgerald J. Correlation between number of eosinophils and reflux index on same day esophageal biopsy and 24 hour esophageal pH monitoring. *Am J Gastroenterol.* 2004;99:801–805. doi:[10.1111/j.1572-0241.2004.04170.x](https://doi.org/10.1111/j.1572-0241.2004.04170.x).
 27. Steiner S, Kernek K, Fitzgerald J. Severity of basal cell hyperplasia differs in reflux versus eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2006;42:506–509. doi:[10.1097/01.mpg.0000221906.06899.1b](https://doi.org/10.1097/01.mpg.0000221906.06899.1b).
 28. Gonsalves N, Policarpo-Nicolas M, Zhang Q, Rao M, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc.* 2006;64:313–319. doi:[10.1016/j.gie.2006.04.037](https://doi.org/10.1016/j.gie.2006.04.037).
 29. Coen A, Petersen K, Clark H, Moore E, Hilden K, Fang J. Prevalence of GERD and allergy in eosinophilic esophagitis. *Gastroenterology.* 2004;126:A447.
 30. Spechler S, Genta R, Souza R. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol.* 2007;102:1301–1306. doi:[10.1111/j.1572-0241.2007.01179.x](https://doi.org/10.1111/j.1572-0241.2007.01179.x).
 31. Calabrese C, Bortolotti M, Fabbri A, et al. Reversibility of GERD ultrastructural alterations and relief of symptoms after omeprazole treatment. *Am J Gastroenterol.* 2005;100:537–542. doi:[10.1111/j.1572-0241.2005.40476.x](https://doi.org/10.1111/j.1572-0241.2005.40476.x).
 32. Caviglia R, Ribolsi M, Gentile M, et al. Dilated intercellular spaces and acid reflux at the distal and proximal oesophagus in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2007;25:629–636.
 33. Mishra A, Hogan S, Brandt E, Rothenberg M. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest.* 2001;107:83–90. doi:[10.1172/JCI10224](https://doi.org/10.1172/JCI10224).
 34. Aceves S, Bastian J, Newbury R, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol.* 2007;102:2271–2279. doi:[10.1111/j.1572-0241.2007.01379.x](https://doi.org/10.1111/j.1572-0241.2007.01379.x).