

Retrospective Study of Fluticasone Propionate and Oral Viscous Budesonide in Children with Eosinophilic Esophagitis

Short Title: Oral Topical Steroids in Eosinophilic Esophagitis

Jacqueline Fable, MD³, Marina Fernandez, MPH¹; Susan Goodine, RD¹; Trudy Lerer, MS²; Wael N. Sayej^{1,4}

¹ Division of Digestive Diseases, Hepatology & Nutrition, Connecticut Children's Medical Center, Hartford, CT;

² Department of Research, Connecticut Children's Medical Center, Hartford, CT;

³ Department of Pediatrics, University of Rochester Medical Center

⁴ Department of Pediatrics, University of Connecticut School of Medicine

Authors

Wael N. Sayej, M.D. - Department of Pediatrics, Digestive Diseases, Hepatology and Nutrition; Connecticut Children's Medical Center, Hartford, CT, United States; University of Connecticut School of Medicine, Farmington CT.

Jacqueline Fable, M.D. – Department of Pediatrics, University of Rochester Medical Center

Marina L. Fernandez M.P.H. - Department of Pediatrics, Digestive Diseases, Hepatology and Nutrition; Connecticut Children's Medical Center, Hartford, CT, United States

Trudy Lerer, MS - Department of Research, Connecticut Children's Medical Center, Hartford, CT, United States

Susan Goodine, RD – Department of Pediatrics, Digestive Diseases, Hepatology and Nutrition; Connecticut Children's Medical Center, Hartford, CT, United States

Funding: Adopt a Friend Grant from the Connecticut Children's Medical Center Foundation and Connecticut Children's Medical Center Strategic Research Funds

Correspondence:

Wael N. Sayej, MD

Connecticut Children's Medical Center

Division of Digestive Diseases, Hepatology and Nutrition

282 Washington Street

Hartford, CT 06106

E-mail wsayej@connecticutchildrens.org

Phone (860) 545-8685; (860) 545-9560

Fax (860) 545-9561

Conflict of Interest: The authors declare no conflict of interest

Transcript Profiling - None

Writing Assistance – All the authors contributed to revisions in the manuscript.

Word Count: 2663

Tables: 3

Figures: 3

ACCEPTED

Abstract

Background: Eosinophilic esophagitis (EoE) is treated with dietary modification and/or pharmacologic management with swallowed topical steroids (TS). Swallowed fluticasone propionate (FP) and oral viscous budesonide (OVB) have proven to be effective in resolving symptoms and reversing histologic changes in children and adults with EoE. There are minimal comparative studies between the two agents.

Aim: To retrospectively compare endoscopic and histologic outcomes following FP versus OVB therapy in children with EoE in our center.

Methods: We performed a retrospective chart review of subjects diagnosed with EoE at a tertiary care center between 2010 and 2015. Inclusion criteria were FP or OVB therapy for ≥ 8 weeks along with pre- and post-treatment endoscopic evaluation. Demographic and clinical features as well as endoscopic and histologic assessment was recorded for comparative analysis. Histologic response was defined as <15 eos/hpf and remission as <5 eos/hpf.

Results: The study included 68 EoE patients (20 FP and 48 OVB) with a mean age of 10.6 ± 5.2 years (range 1-20 years); 81% were male and 68% were Caucasian. No significant demographic or clinical differences were noted between the two study groups. Overall histologic response to TS's was seen in 44/68 (65%) patients. A significantly

greater number of patients achieved histologic response with OVB (36/48, 75%) than with FP (8/20, 40%) ($P = 0.0059$). Mean pre-treatment peak eos/hpf was 46 ± 19 in the FP group vs. 45 ± 23 in the OVB group. Mean post-treatment peak eos/hpf was 20 ± 29 in the FP group vs. 12 ± 16 in the OVB group ($P = 0.002$). There was also a significantly greater difference in the change of absolute eos/hpf from pre- to post-treatment in the OVB group (-33) vs. FP (-18) ($P = 0.047$). A greater number of OVB-treated patients without asthma had a histologic response compared to those with asthma ($P = 0.031$). The response to OVB was not affected by the delivery vehicle, namely sucralose (Splenda®) vs. Neocate® Duocal.

Conclusion: Our data suggest that treatment with OVB leads to better endoscopic and histologic outcomes than FP. Adherence to treatment and history of asthma are major determining factors in the response to treatments. Using Neocate® Duocal as the OVB delivery vehicle is just as effective as sucralose.

Keywords: eosinophilic esophagitis, oral viscous budesonide, swallowed fluticasone propionate, duocal, sucralose, splenda

What is known

Oral topical steroid therapies with oral viscous budesonide (OVB) or fluticasone propionate (FP) are effective treatment options for EoE patients

Sucralose (Splenda®) is the delivery vehicle of choice for oral viscous budesonide

What is new

Oral viscous budesonide is more effective than inhaled fluticasone propionate in children with EoE

The absence of asthma is a major determining factor in achieving response or remission

Neocate® Duocal is just as effective as Sucralose for OVB delivery to the esophageal mucosa

Introduction

Eosinophilic esophagitis (EoE) is an emerging illness of the esophagus with both active and chronic inflammation that can lead to long-term sequelae of fibrosis and esophageal strictures. It is an allergy-associated disease, characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil infiltration into the esophageal epithelium (>15 eosinophils per high-power field (eos/hpf)). EoE has garnered increased attention since its recognition as a separate entity from reflux disease in 1993 (1, 2), and often diagnosed before a child's sixth birthday. The incidence and prevalence of EoE have increased dramatically over the past 20 years. (3) In children incidence and prevalence are currently estimated to be 0.7-10/100,000 and 0.2-43/100,000 per person-year, respectively (3).

Patients with EoE typically present with feeding difficulties, failure to thrive, vomiting, pain and difficulty with swallowing, and food impactions in the esophagus (4). The goals of therapy are to resolve symptoms of esophageal dysfunction, prevent complications from long-standing EoE, and maintain histologic remission. Therapeutic options include dietary modifications and topical steroids. Dietary management includes elemental diets (5, 6), directed elimination diets (7-10), and a 6-food elimination diet (10-12). When followed, elimination diets can be highly effective; however, poor compliance is often an issue that prevents symptomatic and histologic resolution of EoE (13, 14). If dietary

restriction is not practical or adherence to food elimination is not effective, swallowed topical steroids are utilized (fluticasone propionate or oral viscous budesonide). In many centers, TS's are the first-line treatment for eosinophilic esophagitis.

Both swallowed fluticasone propionate (FP) and oral viscous budesonide (OVB) are proven to be effective in resolving symptoms and reversing histologic changes. Albert et al. retrospectively compared the efficacy of FP and OVB in 75 patients (age 2-64 years, mean 33 years) and showed an overall response rate of 51% and no difference in response to FP (48%) vs. OVB (56%) (15). However, no study has yet compared the 2 treatment options, retrospectively or prospectively, in children with EoE. Fluticasone is puffed into the mouth by a metered-dose inhaler and then swallowed (16). This form of topical steroid treatment has a number of benefits, including its ease of administration and limited systemic side effect profile. Studies looking at FP use in children with eosinophilic esophagitis have reported significant improvement in both symptoms and histologic findings (17-20). Budesonide is another common steroid that has been used for treatment of EoE (21-24). Dellon et al. showed that viscous budesonide was superior to swallowed nebulized budesonide solution in terms of histologic improvement, although both therapies resulted in similar clinical improvement (25). Budesonide mixed in sucralose has been shown to be effective and safe in children with EoE (26). Early comparisons using sucralose (23, 24) or Neocate® Nutra (27) as delivery vehicles for viscous budesonide suggested similar efficacy in terms of histological and clinical improvement.

Our goals in this study were to retrospectively compare treatment outcomes in children who received oral topical steroid therapy at our center, identify any factors that influenced the success or failure of therapy, and determine whether an alternative delivery vehicle for budesonide, namely Neocate® Duocal, was just as effective as sucralose in achieving histologic improvement.

Methods

We performed a retrospective chart review of patients with documented EoE, defined endoscopically as greater than 15 eos/hpf on esophageal biopsies with normal gastric and duodenal biopsies, who were treated with OVB or FP at Connecticut Children's Medical Center (CCMC) between 2010 and 2015. The primary outcome measure was histological response, defined as a decrease in peak eosinophil count to less than 15 eos/hpf after a minimum of 8-12 weeks of therapy with FP or OVB. Patients were treated with FP or OVB with age-dependent dosing consistent with current recommendations (28, 29). The secondary outcome was a comparison of the efficacy of OVB when using 2 different delivery vehicles (Duocal vs. sucralose). This study was approved by the institutional review board at CCMC, Hartford, CT (IRB #14-113).

Patient Demographics and Clinical Data

The OVB- and FP-treated groups were compared in terms of their demographic, endoscopic, and histological characteristics. Demographic characteristics included age,

gender, race, height, weight, and body mass index (BMI). Clinical characteristics included prior therapies (proton pump inhibitors, H2 blockers); simultaneous dietary elimination (directed dietary elimination, dairy elimination, 6-food elimination diet); history of other atopic diseases (asthma, eczema, seasonal or environmental allergies, and allergic rhinitis); and history of medication and food allergies. Characteristics on initial endoscopic evaluation leading to TS therapy included normal appearance as well as the presence of furrows, rings, white specks/plaques, strictures, luminal narrowing, crepe-paper esophagus, or erosions. Histological characteristics included peak eos/hpf and basal layer hyperplasia.

Inclusion Criteria

We reviewed the charts of 279 active patients, ages 1-20, with EoE documented by endoscopic biopsy. Eighty-four patients who were treated with OVB or FP at CCMC between 2010 and 2015 were identified but only 68 were included in this study. Sixteen patients were excluded due to insufficient data. Patients were required to have undergone upper endoscopy with biopsy both prior to treatment initiation as well as at least 8-12 weeks following treatment with FP or OVB. The choice of topical steroids was determined based on patient preference, provider preference, history of failing a previous steroid regimen, or insurance coverage. A total of 65/68 patients received high dose PPI therapy prior to starting the steroid therapy and only 3/68 were not treated with high dose PPI therapy due to severity of symptoms and endoscopic findings. All patients received concomitant high dose PPI therapy during treatment with the steroid therapy. Individuals

with various comorbidities including inflammatory bowel disease, celiac disease, and H. pylori gastritis were excluded from the study.

Treatment Protocols

At CCMC, children from 1-10 years are treated with fluticasone 110 µg/puff inhaler, 2 puffs twice per day. Children older than 11 are treated with fluticasone 220 µg/puff inhaler, 2 puffs twice per day. Patients treated with FP, regardless of age, were instructed not to use a spacer.

The dosage of OVB in this study was 0.5 mg BID (0.25 mg/2 ml or 0.5 mg/2 ml respules) in children aged 1-10 years, and 1 mg BID (one 1 mg/2 ml respule or two 0.5 mg/2 ml respules) in children aged 11-20 years. Patients were instructed to prepare OVB by opening the liquid budesonide respules and mixing the contents with 5 packets of sucralose (Splenda®), then swallowing the mixture slowly over 5-10 minutes. This was done twice daily (total of 10 packets of sucralose per day). From 2012 to 2015, Neocate® Duocal was used as a delivery vehicle due to long-term safety concerns about using 10 packets of sucralose per day. Patients were instructed to mix one tablespoon of Duocal with 1 or 2 respules of budesonide and to swallow slowly over 5-10 minutes. A subset of patients, who were not willing to use the sucralose or Duocal, used other regimens (2 packets of Truvia, 2 packets of Stevia, one tablespoon of pasteurized maple syrup or honey). All patients treated with OVB or FP were instructed to abstain from eating or

drinking for 30 minutes following medication administration, and to drink something after 30 minutes to rinse the medications.

Outcomes

The primary outcome was histological response, defined as a decrease in peak eosinophil count to less than 15 eos/hpf after 8-12 weeks of therapy with FP or OVB. Complete remission was defined as <5 eos/hpf. Patients who continued to have >15 eos/hpf were considered to be treatment failures. Secondary outcomes included endoscopic visualization, presence of side effects from TS, and self-reported adherence or non-adherence (<50%) with TS. Endoscopic improvement was based on resolution of furrows, white specks or trachealization. We also compared histologic outcomes between the different OVB delivery vehicle subgroups (sucralose or Neocate® Duocal).

Statistical Analysis

Groups were compared using t-tests for continuous variables and chi-square or exact tests for categorical variables. Subgroup analyses compared differences in histological outcomes between Sucralose and Neocate® Duocal as the delivery vehicles for OVB and between patients with and without asthma.

Results:

Demographic and Clinical Characteristics of Study Groups

Of the 279 patients aged 1-20 years who had EoE documented by endoscopic biopsy, 84 were treated with swallowed FP or OVB at CCMC between 2010 and 2015. Sixty-eight patients were included in this study and 16 were excluded due to insufficient data. Patient characteristics and demographics are presented in Table 1. There were no significant differences with regard to demographic characteristics with the one exception of requiring secondary therapy. Patients who failed initial therapy and required a treatment course with a second steroid were more likely to have received FP as the initial treatment ($P=.005$). Three patients (6%) failed OVB and were switched to FP while 7 (35%) patients switched from FP to OVB.

Response to Treatment

The overall response rate to TS therapy was 44/68 (65%). A significantly greater number of patients responded to OVB (36/48, 75%) compared with FP (8/20, 40%) ($P = 0.0059$, odds ratio 4.5, 95% confidence interval 1.1-2.5) (Figure1). Remission was achieved by a higher percentage of patients in the OVB group (26/48, 54%) than the FP group (7/20, 35%), but this was not statistically significant ($P = 0.1$). The prevalence of atopic disease (Asthma, eczema, environmental and seasonal allergies) and food allergies was similar in both groups (Table 1). Of the patients treated with OVB, those without asthma were more likely to have a histologic response than those with asthma ($P = 0.031$). This difference was not observed in the FP group. Lastly, most patients were treated with high dose PPI

therapy prior to starting steroid therapy except for 3 patients (2 in the FP group and 1 in the OVB group). We included them because of their disease severity based on symptoms and endoscopic findings and did not believe that they would respond to PPI therapy alone. They were treated with high dose PPI therapy concomitantly with their steroid therapy. These 3 patients continue to be on steroid therapy.

Endoscopic findings are summarized in Table 2. Overall, there was a significant improvement or complete resolution of furrows and eosinophilic exudates after treatment with the topical steroids ($P = <0.0001$). There was a more significant and robust resolution of characteristic endoscopic findings in the OVB group compared to the FP group, especially regarding the resolution of furrows ($P = <0.0001$ vs. $P = 0.1967$, respectively).

Histologically, there was no significant difference in the pre-treatment peak eosinophil count between the FP and OVB groups ($P = 0.6427$) (Figure 2A). Post-treatment peak eosinophil counts were significantly lower in the OVB group (12 eos/hpf) compared to the FP group (30 eos/hpf) ($P = 0.02$) (Figure 2B). Additionally, while the peak eosinophil counts were significantly lower after treatment than before treatment in both groups ($P = <0.0001$ for OVB, $P = 0.0265$ for FP), the decrease in peak eos/hpf was significantly higher in the OVB group than in the FP group (Figure 2C and 2D). Lastly, the change in absolute eosinophil counts from pre- to post-treatment was significantly greater in the OVB group (-33 eos/hpf) than in the FP group (-18 eos/hpf) ($P = 0.047$) (Figure 2E).

Basal cell hyperplasia (BCH) was noted in all patients and summarized in Table 3. Overall, there was a significant improvement in BCH, especially those with marked/severe BCH, from pre- (75%) to post- (21%) treatment, $P = <0.0001$. Pre-treatment BCH was severe in 85% of patients who received FP and 71% of those who received OVB ($P = 0.2285$). Post-treatment BCH was severe in 30% of patients who received FP compared to 16% of those who received OVB ($P = 0.6352$). BCH was significantly improved from pre- (85%) to post- (30%) treatment in patients who received FP ($P = 0.0003$) and from pre- (71%) to post- (16%) treatment in patients who received OVB ($P = <0.0001$).

Delivery Vehicle for OVB

A total of 11 (23%) patients mixed their budesonide with Duocal, 33 (69%) mixed it with sucralose, and 4 (8%) mixed it with other vehicles (truvia, stevia, maple syrup, or honey) (Figure 3A). The type of delivery vehicle, namely sucralose, Duocal or other, did not have a statistically significant impact on histologic response. The response rates for these 3 groups were 73%, 76%, and 50%, respectively, and remission rates were 55%, 58%, and 50%, respectively (Figure 3B).

Adherence to therapy

Twelve of the 68 patients (18%) self-reported poor adherence and were less likely to achieve histologic response following treatment. Non-adherence was reported by 7/48

(15%) patients in the OVB group compared to 5/20 (25%) patients in the FP group (NS). Histologic response was achieved in 43/56 (77%) adherent patients compared to 1/12 (8%) non-adherent patients, ($P = <0.001$). Surprisingly, there was no difference in age between the adherent vs. non-adherent patients in both the OVB and FP groups.

Discussion

Treatment of eosinophilic esophagitis is limited, and continues to pose a challenge for physicians and patients. The choice of which swallowed TS to use is usually determined jointly by patients and their physicians. Since the recognition of EoE, there have been many published studies on TS, elemental diets, and dietary elimination regimens.

Until recently, there has never been a retrospective or prospective comparison of response to the 2 most commonly used TSs, fluticasone propionate and budesonide. Albert et al. recently reported on a retrospective comparison of 75 patients (children and adults, aged 2-64 years, median 33 years) who received fluticasone or budesonide (15). The response rate was 51% overall, and did not differ significantly between the 2 groups (48% in the FP group and 56% in the OVB group). In previous studies, retrospective and prospective, the response rate to budesonide was reported to be 80%-87% (23, 26). Response rates to fluticasone have been reported to be around 40%-62% (17, 30, 31). The present study, although retrospective, is the first to compare treatment response to FP vs. OVB in children. Our overall response rate was 65%. The response rate was 75% in the

OVB group vs. 40% in the FP group ($P = 0.0059$), consistent with the published literature. The remission rates were 54% and 35% in the OVB and FP groups, respectively. In comparison with the study of Albert et al., we demonstrated a higher response rate and a significant difference in response between the FP and OVB groups.

Endoscopically, there was significant improvement and/or resolution in visual findings (furrows, white specks or trachealization) after treatment with FP and OVB, but these results were more robust in the OVB group compared to the FP group. Histologically, OVB was superior to FP in achieving higher response and remission rates, lower post-treatment peak eosinophil counts, and greater reduction in absolute eosinophil counts. There was significant improvement in BCH in both groups from pre- to post-treatment. It is likely that the higher response and remission rates with OVB are due to better surface contact of the viscous solution (OVB) with the esophageal mucosa compared to the swallowed inhalant (FP). It is also possible that patients were not swallowing the FP properly.

Both medications have been shown to be safe, with similar side effect profiles. While Harel et al. showed, in a retrospective study, that OVB led to suboptimal adrenocorticotrophic hormone stimulation test results in 6/14 (43%) patients (32), Philla et al. recently showed that swallowed oral topical steroid therapy with OVB or FP did not suppress adrenal function (33). In our study, we did not have any data on the effects of these steroids on the adrenal axis. Only 2 patients on FP developed thrush and one developed candida esophagitis, while only one patient on OVB developed thrush

With regard to the delivery vehicle, the safety of long-term sucralose use is of concern. In this study, we showed that Duocal was just as effective as sucralose. Although Duocal does not contain any protein, it is not considered to be a hypoallergenic supplement. Additionally, it contains cornstarch and coconut oil, which makes it contraindicated in patients with allergies to corn and coconut. Neocate® Nutra, a hypoallergenic supplement, has been shown to be just as effective as sucralose (27). There may be cost and insurance coverage issues associated with Nutra, however, and Duocal, pasteurized honey, or maple syrup may be excellent alternatives for patients placed on OVB.

There are many strengths to our study. This is the first study in pediatrics to retrospectively compare the 2 most commonly used EoE therapies, FP and OVB. For all 68 patients included in the study, histologic and endoscopic data were completely available and documented.

The major limitation with our study is that it uses a retrospective cohort design to compare two different treatment options. Because of this, selection bias is likely. Specifically, patients could have been prescribed fluticasone vs budesonide due to provider preference, a past history of treatment success or failure, patient preference, insurance issues, or other reasons that could impact our measured response rates. Similarly, the dose of steroids prescribed is lower than current practices, and compliance was not measured and could be difficult to definitively discern from the medical records.

Butz et al. (34) and Gupta et al.(35) showed that higher doses of fluticasone propionate and oral budesonide suspensions were more effective in 2014. Most of our patients included in this study were treated with standard of care that was based on the 2011 eosinophilic esophagitis consensus recommendations for children and adults(36). Additionally, there were 10 patients that were included in the study that were not steroid naïve. We included those patients in the study to show that failing one steroid regimen is not an indication that they will fail the other. Lastly, 3 patients were not treated with PPI therapy prior to starting steroid therapy and were included in the study. These 3 patients continue to be on steroid therapy and PPI therapy, yet, continue to have persistent inflammation. Two patients have asthma and one patient has non-compliance issues.

In summary, oral viscous budesonide may be a more effective treatment choice than swallowed fluticasone propionate in children with EoE. It leads to better histologic and endoscopic response and remission. Additionally, of patients we could confirm to be non-compliant, this was a major contributing factor in failure to achieve response or remission. The absence of asthma is a significant indicator for achieving response. Lastly, Duocal is just as effective as sucralose as a delivery vehicle for budesonide.

Figures and Tables:

Figure 1: Response and remission rates with topical steroids.

Figure 2: Comparison of pre- and post-treatment peak eosinophil counts. (A) FP vs. OVB pre-treatment eos/hpf; (B) FP vs. OVB post-treatment eos/hpf; (C) absolute change in peak eos/hpf from pre- to post-treatment; (D) FP pre- vs. post-treatment peak eos/hpf; (E) OVB pre- vs. post-treatment peak eos/hpf.

Figure 3: OVB delivery vehicle. (A) Delivery vehicle; and (B) response and remission rates based on delivery vehicle.

Table 1: Demographic data of patients treated with TS (FP or OVB).

Table 2: Endoscopic findings pre- and post-treatment with FP vs. OVB

Table 3: Histology results pre- and post-treatment with FP vs. OVB

Figure 1

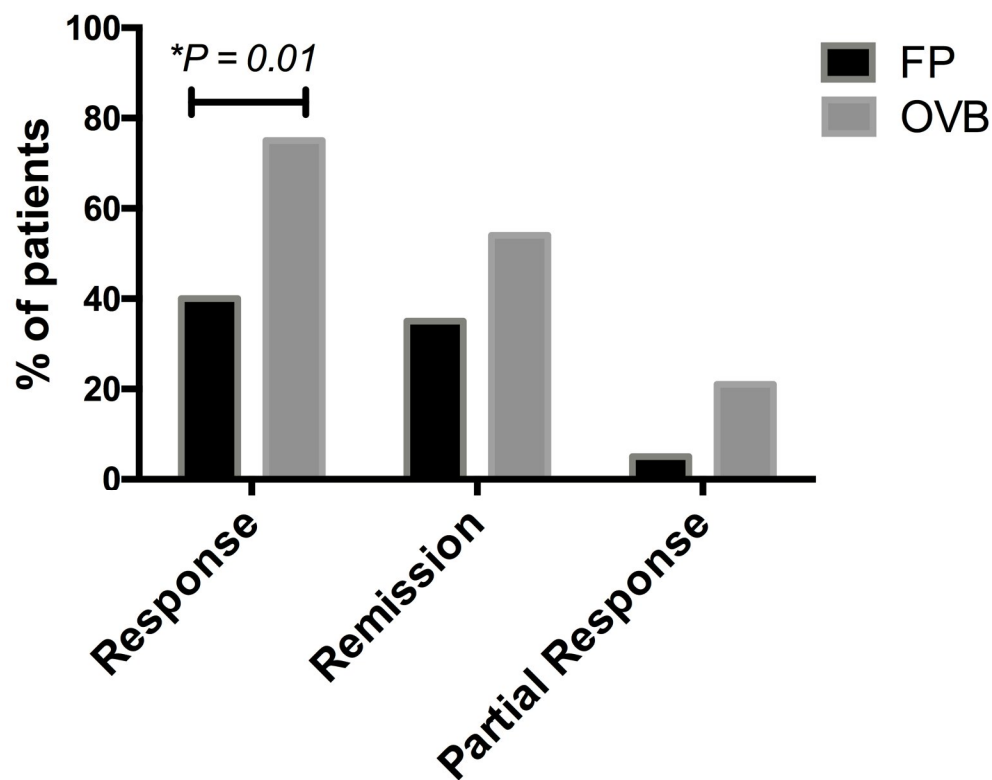


Figure 2

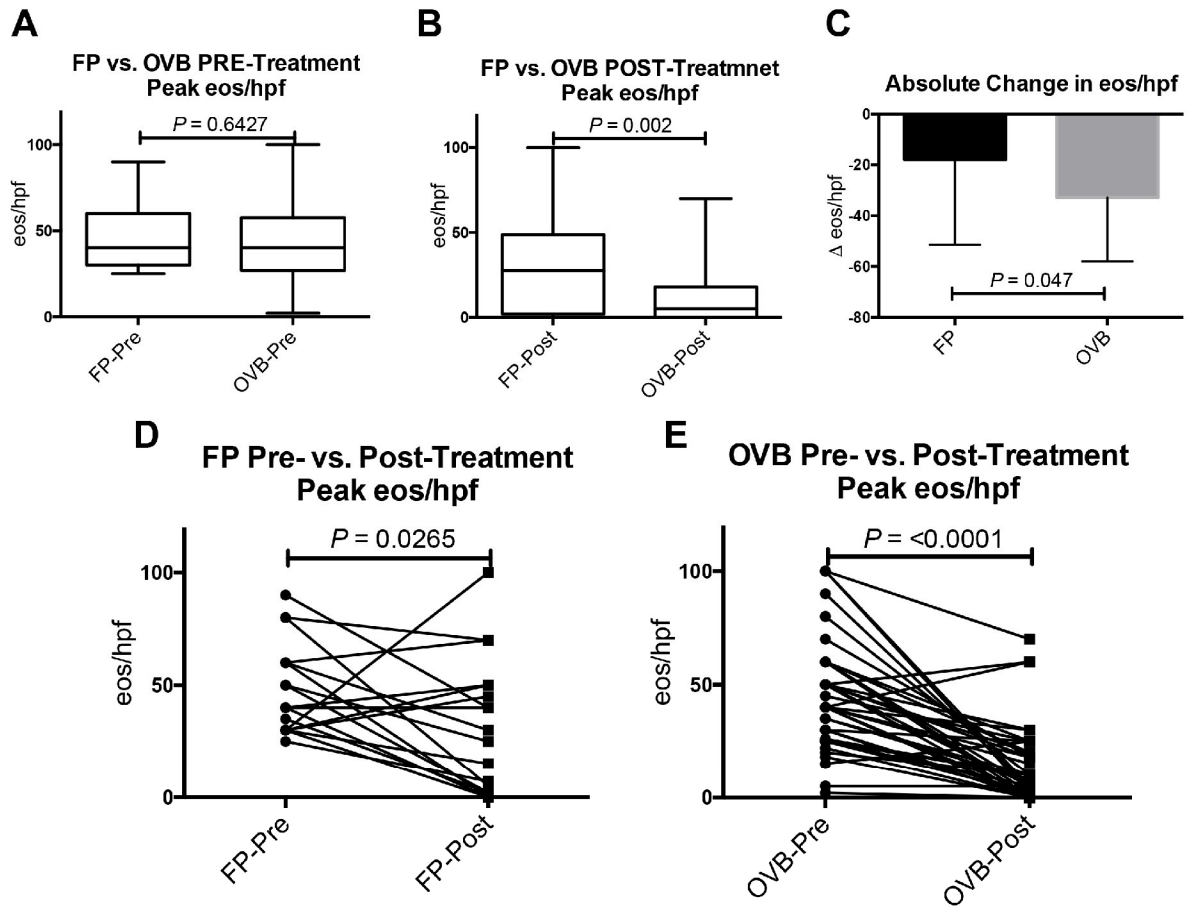


Figure 3

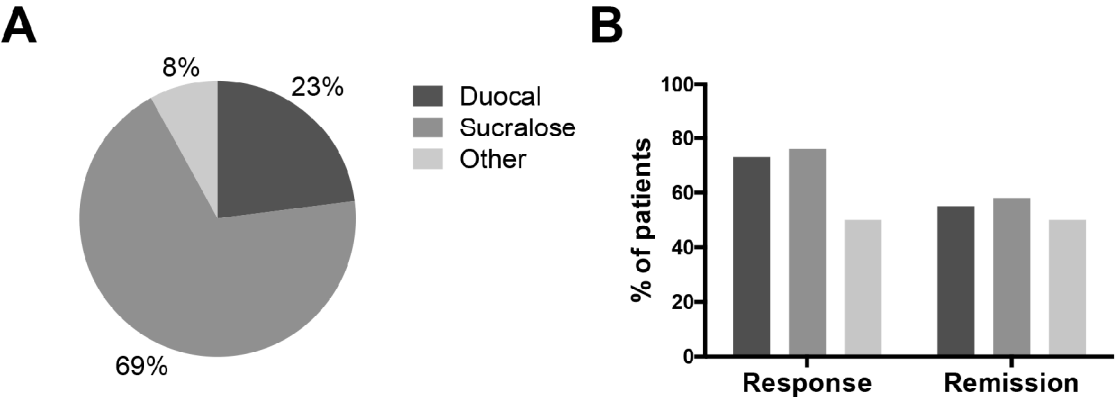


Table 1: Demographic and Clinical Characteristics of Study Groups

	FP	OVB	Total	<i>P</i> value*
N	20 (29%)	48 (71%)	68 (100%)	
Age (Mean $\pm$ SD, Range)	12 $\pm$ 4 (1-20)	10 $\pm$ 6 (1-20)	11 $\pm$ 5 (1-20)	0.09
Gender (n, % Male)	18 (90)	37 (77%)	55 (81%)	0.3168
BMI	20 $\pm$ 4	21 $\pm$ 6	20 $\pm$ 6	0.57
Race (Caucasian)	17 (85%)	32 (67%)	49 (72%)	0.6887
Allergy History				
Food allergies	12 (60%)	29 (60%)	41 (60%)	1
Environmental allergies	5 (25%)	11 (23%)	16 (24%)	1
Seasonal allergies	4 (20%)	8 (7%)	12 (18%)	0.722
Medication allergies	5 (25%)	15 (31%)	20 (29%)	0.7223
Asthma	7 (35)	21 (44)	28 (41)	0.5041
Treatment Data				
Medication therapies prior to TS	19 (95%)	48 (100%)	67 (99%)	0.2941
High dose PPI	18 (90%)	47 (98%)	65 (96%)	0.2047
H2 blocker	3 (15%)	9 (19%)	12 (18%)	1
Dietary modifications prior to TS	19 (95%)	41 (85%)	60 (88%)	0.4205
Treatment Duration (weeks)	23 $\pm$ 13	19 $\pm$ 11	20 $\pm$ 12	0.2814
Non-compliance	5 (25%)	7 (15%)	12 (18%)	0.3157
*Secondary therapy (n, %)	7 (35%)	3 (6%)	10 (15%)	0.005

Data expressed as mean $\pm$ standard deviation or number and frequency (%)

BMI = body mass index, TS = topical steroids, PPI = proton pump inhibitor, H2 blocker = histamine receptor blocker.

*Secondary therapy means that patients who were treated and failed FP were treated with OVB and vice versa.

* *P* values computed using t-tests for numerical variables and Chi square test for categorical variables

Table 2: Endoscopic findings pre- and post-treatment with FP vs. OVB

	FP (n = 20)			OVB (n = 48)			Total (n = 68)		
	Pre-	Post-	P value	Pre-	Post-	P value	Pre-	Post-	P value*
Abnormality (n, %)	18 (90)	12 (60)	0.0285	44 (92)	22 (46)	<0.0001	62 (91)	34 (50)	<0.0001
Furrows (n, %)	14 (79)	10 (50)	0.1967	29 (60)	11 (23)	<0.0001	43 (63)	21 (31)	0.0002
Rings/trachealization (n, %)	5 (25)	4 (20)	0.705	3 (6)	4 (8)	0.6947	8 (12)	8 (12)	1
White specks/plaques (n, %)	10 (50)	1 (5)	0.0014	16 (33)	2 (4)	0.0003	26 (38)	3 (4)	0.0003

*P values computed using Chi-square test

Data expressed as number and frequency (%)#

Table 3: Histology results pre- and post-treatment with FP vs. OVB

	FP (n=20)	OVB (n=48)	Total (n=68)	P value
Histology Data				
Pre-treatment eos/hpf	48 ± 19	45 ± 23	46 ± 22	0.64
Post-treatment eos/hpf	30 ± 29	12 ± 16	17 ± 22	0.016
Change in eos/hpf	(18) ± 34	(33) ± 25	(28) ± 29	0.047
Response = <15 eos/hpf (n, %)	8 (40)	36 (75)	44 (65)	0.0111
Remission = <5 eos/hpf (n, %)	7 (35)	26 (54)	33 (49)	0.3
Basal Cell Hyperplasia				
Pre-treatment				
None/mild (n, %)	2 (10)	11 (23)	13 (19)	
Moderate (n, %)	1 (5)	3 (6)	4 (6)	
Marked/severe (n, %)	17 (85)	34 (71)	51 (75)	
Post-treatment				
None/mild (n, %)	13 (65)	34 (71)	47 (69)	
Moderate (n, %)	1 (5)	6 (13)	7 (10)	
Marked/severe (n, %)	6 (30)	8 (16)	14 (21)	

P values computed using t-tests for numerical variables and Chi square test for categorical variables

Data expressed as number ± SD or number and frequency (%). Values in parenthesis are negative values.

REFERENCES

1. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci*. 1993;38(1):109-16.
2. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503-12.
3. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. *Journal of pediatric gastroenterology and nutrition*. 2013;57(1):72-80.
4. Liacouras CA, Spergel J, Guber LM. Eosinophilic esophagitis: clinical presentation in children. *Gastroenterology clinics of North America*. 2014;43(2):219-29.
5. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *The American journal of gastroenterology*. 2003;98(4):777-82.
6. Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *The American journal of gastroenterology*. 2013;108(5):759-66.
7. Gonzalez-Cervera J, Molina-Infante J, Lucendo AJ. Skin testing-directed elimination diet - is 100% efficacy conceivable in eosinophilic esophagitis? *Pediatric*

allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2015.

8. Molina-Infante J, Martin-Noguerol E, Alvarado-Arenas M, Porcel-Carreno SL, Jimenez-Timon S, Hernandez-Arbeiza FJ. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;130(5):1200-2.

9. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2005;95(4):336-43.

10. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130(2):461-7 e5.

11. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol*. 2013;131(3):797-804.

12. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2006;4(9):1097-102.

13. Warners MJ, Vlieg-Boerstra BJ, Bredenoord AJ. Elimination and elemental diet therapy in eosinophilic oesophagitis. *Best practice & research Clinical gastroenterology*. 2015;29(5):793-803.
14. Wechsler JB, Schwartz S, Amsden K, Kagalwalla AF. Elimination diets in the management of eosinophilic esophagitis. *Journal of asthma and allergy*. 2014;7:85-94.
15. Albert D, Heifert TA, Min SB, Maydonovitch CL, Baker TP, Chen YJ, et al. Comparisons of Fluticasone to Budesonide in the Treatment of Eosinophilic Esophagitis. *Dig Dis Sci*. 2016.
16. Gonsalves N. Steroids versus dietary therapy for the treatment of eosinophilic esophagitis. *Current opinion in gastroenterology*. 2014;30(4):396-401.
17. Sayej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. *Journal of pediatric gastroenterology and nutrition*. 2009;49(4):393-9.
18. Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *The Journal of pediatrics*. 2009;154(1):96-100.
19. Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2008;6(2):165-73.

20. 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(5):1313-9.
21. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology*. 2010;139(5):1526-37, 37 e1.
22. Straumann A, Conus S, Degen L, Frei C, Bussmann C, Beglinger C, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2011;9(5):400-9 e1.
23. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *The American journal of gastroenterology*. 2007;102(10):2271-9; quiz 80.
24. Aceves SS, Dohil R, Newbury RO, Bastian JF. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2005;116(3):705-6.
25. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012;143(2):321-4 e1.
26. 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(2):418-29.

27. Rubinstein E, Lee JJ, Fried A, Logvinenko T, Ngo P, McDonald D, et al. Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children. *Journal of pediatric gastroenterology and nutrition*. 2014;59(3):317-20.
28. Contreras EM, Gupta SK. Steroids in pediatric eosinophilic esophagitis. *Gastroenterology clinics of North America*. 2014;43(2):345-56.
29. Furuta GT. Eosinophilic esophagitis: update on clinicopathological manifestations and pathophysiology. *Current opinion in gastroenterology*. 2011;27(4):383-8.
30. Alexander JA, Jung KW, Arora AS, Enders F, Katzka DA, Kephardt GM, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2012;10(7):742-9 e1.
31. Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006;131(5):1381-91.
32. Harel S, Hursh BE, Chan ES, Avinashi V, Panagiotopoulos C. Adrenal Suppression in Children Treated With Oral Viscous Budesonide for Eosinophilic Esophagitis. *Journal of pediatric gastroenterology and nutrition*. 2015;61(2):190-3.
33. Philla KQ, Min SB, Hefner JN, Howard RS, Reinhardt BJ, Nazareno LG, et al. Swallowed glucocorticoid therapy for eosinophilic esophagitis in children does not suppress adrenal function. *Journal of pediatric endocrinology & metabolism : JPEM*. 2015;28(9-10):1101-6.

34. Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, et al. Efficacy, Dose Reduction, and Resistance to High-Dose Fluticasone in Patients With Eosinophilic Esophagitis. *Gastroenterology*. 2014;147(2):324-33 e5.
35. Gupta SK, Vitanza JM, Collins MH. Efficacy and Safety of Oral Budesonide Suspension in Pediatric Patients With Eosinophilic Esophagitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2014.
36. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011.