

Comparisons of Fluticasone to Budesonide in the Treatment of Eosinophilic Esophagitis

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Abstract

Background Topical steroids are first-line treatment agents for eosinophilic esophagitis; however, some studies have demonstrated modest efficacy in inducing histologic remission.

Aims The aim of this study was to determine response to two topical steroids (fluticasone and budesonide), compare their efficacy, and examine patient characteristics which could predict non-response to topical steroids.

Methods We performed a retrospective review of an established EoE registry. Inclusion criteria were patients >1 year of age who were diagnosed with EoE as defined by the most recent consensus guidelines. All patients were treated with an 8-week course of either swallowed fluticasone or viscous budesonide. Responders were defined as achieving <15 eosinophils per high-power field (eos/hpf) in both proximal and distal esophageal biopsies. Demographic, clinical, endoscopic, and histologic features were examined.

Results The study cohort included 75 EoE patients with a median age of 33 years (range 2–64 years), 71 % adults, 84 % male, and 76 % Caucasian. Overall histologic response rate to topical steroids was 51 %, while clinical

response was 71 %. There was no significant differences in histologic response to treatment between children and adults (68 vs. 44 %, $p = 0.111$). There was no significant difference in response between males and females (47 vs. 73 %, $p = 0.191$) and between the two types of steroids (48 vs. 56 %, $p = 0.632$). Responders and non-responders were similar in clinical presentation and baseline endoscopic findings. Following treatment, responders had significantly less peak proximal (4.0 ± 4.4 vs. 46 ± 53 , $p < 0.001$) and distal eosinophil counts (3.5 ± 3.8 vs. 60 ± 47 , $p < 0.001$) compared to non-responders. There were no predictors of response to steroids identified.

Conclusions Histologic response to treatment was observed in approximately half the cohort, while more than two-thirds experienced clinical response to topical steroids. Response was similar between fluticasone and budesonide. Given the lack of differences in clinical presentation or endoscopic features, predictors of non-response were not seen.

Keywords Topical steroids · Fluticasone · Budesonide · Eosinophilic esophagitis · Predictors

Abbreviations

EoE	Eosinophilic esophagitis
PPI	Proton-pump inhibitor
eos/hpf	Eosinophils per high-powered field
PPI-REE	Proton-pump inhibitor-responsive esophageal eosinophilia

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition characterized clinically by symptoms of esophageal dysfunction and histologically by

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dense eosinophilic infiltration [1, 2]. Although symptoms differ between adults and children, treatment is similar which includes removing the offending allergen and reducing esophageal inflammation. The most commonly prescribed medications in the management of EoE are topical corticosteroids. Two formulations are currently available for use in clinical practice, swallowed aerosolized fluticasone and oral viscous budesonide, although no consensus exists to date on how to define histologic response or remission to treatment.

The first studies using aerosolized fluticasone were open-labeled trials that demonstrated very favorable histologic responses (>90 %) [3–5]. Since then, several randomized controlled trials have reported a more modest complete histologic response (15–62 %) to aerosolized fluticasone, which varies depending on the histologic endpoint used (i.e., ≤ 1 , ≤ 5 , ≤ 7 , or ≤ 15 eosinophils/high-power field [6–9]. The response to budesonide in clinical trials has been higher (52–86 %), although there are no comparative studies with the two formulations [10–13]. In an open-label randomized study using nuclear scintigraphy images to compare nebulized and viscous budesonide, the distribution of the viscous solution was greater in the esophagus, had higher mucosal contact time, and had a histologic response superior to nebulized budesonide [14].

Despite EoE being an allergic and immune-mediated condition, response to topical steroids is lower than would be expected. Predictors of non-response to treatment have not been well studied, and if known, could help guide therapy. The aims of this study were to determine histologic response to each steroid, compare their efficacy, and examine patient characteristics which could predict non-response to topical steroids.

Methods

Study Population

We performed a retrospective review of patients who were enrolled into an EoE registry at Walter Reed National Military Medical Center from April 2008 to October 2013. Inclusion criteria were patients >1 year of age who were diagnosed with EoE, as defined by most recent consensus guidelines [1, 2]. All cases had an esophagogastroduodenoscopy (EGD) with esophageal biopsies performed at Walter Reed before and after treatment with a topical corticosteroid for 8 weeks. In all patients, a total of at least eight samples using large-capacity biopsy forceps (Boston Scientific, Natick, MA) were taken to improve diagnostic accuracy: four biopsies from the proximal esophagus, defined as approximately 15 cm from the gastro-esophageal junction, and four biopsies from the distal esophagus,

approximately 3 cm above the gastro-esophageal junction. Subjects were excluded if they had not received at least an 8-week trial of high-dose PPI prior to index endoscopy, were diagnosed with proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE), had been previously treated with swallowed topical steroids, did not complete an 8-week course of topical corticosteroids after diagnosis of EoE, or did not have an EGD with esophageal biopsies before or after 8 weeks of corticosteroid treatment. All EoE patients signed informed consent or assent to participate in the registry. This study was approved by the Institutional Review Board of Walter Reed.

Treatment with Corticosteroids and Primary Endpoint

Patients received aerosolized fluticasone or viscous budesonide, depending on patient preference and the treating gastroenterologist. Dosing was dependent on patient age. Adults (≥ 18 years) received either fluticasone 440 mcg twice daily or budesonide 1 mg twice daily. Children received fluticasone 220 mcg twice daily or budesonide 0.5 mg twice daily. Those receiving fluticasone were instructed to puff and swallow the medication twice daily. Patients receiving budesonide were instructed to mix the respule with either Splenda or honey until a viscous consistency is formed and swallow. Patients were instructed not to eat or drink for at least 30 min after drug administration. All patients underwent an EGD with esophageal biopsies after 8 weeks of treatment. The primary endpoint measured was histologic response, defined as achieving <15 eos/hpf in both proximal and distal esophageal biopsies following treatment. Esophageal dilation was performed on patients with a symptomatic stricture. Method of dilation and size of dilator were dependent on the endoscopist.

Data Collection

Data were collected from the military electronic medical record system, the Armed Forces Health Longitudinal Technology Application (AHLTA), and from a registry of EoE patients. All patients were evaluated by the authors of this study, and their charts were reviewed to abstract the data. We recorded patient demographics (age, race, gender), clinical symptoms prior to treatment (dysphagia, food impaction, heartburn in adults and in children, additional symptoms of regurgitation, vomiting, abdominal pain), dichotomous subjective improvement (yes/no) following treatment with steroids, baseline EGD findings (concentric rings, longitudinal furrows, white plaques, strictures), baseline and follow-up peak eosinophil counts on esophageal biopsies, whether pre-treatment dilation was performed, and therapeutic regimen (medication and dosage).

We also categorized phenotype based on baseline endoscopic features. The presence of furrows and white plaques was categorized as an inflammatory phenotype, whereas the presence of rings and strictures was considered fibrostenotic phenotype. Eosinophil counts were recorded as the maximum number of eos/hpf. All slides were re-reviewed by a single gastrointestinal pathologist, blinded to the method of treatment, who generated the peak eosinophil counts used for this study. A high-powered field was considered 40 $\times$ magnification on our microscopes, which measured 0.24 mm². Currently, there is no consensus on what eosinophil count determines a response to treatment. For the purpose of this analysis, patients with an eosinophil count <15 eos/hpf in both the mid-proximal and distal esophagus were defined responders of treatment.

Statistical Analysis

Statistical software package IBM SPSS version 21 (IBM, Armonk, New York) was used to collate and analyze the data. Descriptive summary data are expressed as frequency and percentage, mean and standard deviation, or median and range. Comparisons of responders to non-responders were made with Fisher's exact test or two-sample independent *t* test. A Mantel–Haenszel test was used to test if dilation was a confounder to clinical response. A probability of <0.05 was considered statistically significant.

Results

Three hundred and seven patients with suspected EoE were reviewed, 185 patients did not have at least 2 EGDs performed at our institution at baseline and following 8 weeks of treatment with topical steroids, 13 patients were not treated with topical steroids, and 34 patients were diagnosed with PPI-REE. The study cohort consisted of 75 EoE patients (19 pediatric and 56 adult) who met the inclusion criteria. The median age was 33 years (range 2–64 years), 75 % adults, 84 % male, and 76 % Caucasian. Clinical symptoms at baseline were food impaction (29 %), dysphagia (85 %), and heartburn (24 %) with baseline EGD findings consisting of longitudinal furrows (79 %), concentric rings (59 %), and white plaques (31 %; Table 1). At index, 64 % of the cohort had fibrostenotic features and 36 % had inflammatory features. Aerosolized fluticasone was used in 63 % of patients, and the remaining 37 % were treated with budesonide. Pre-treatment dilation was performed in 23 % of patients who received fluticasone and in 52 % given budesonide.

When defining histologic response as achieving <15 eos/hpf in both proximal and distal biopsies, the overall response rate to topical steroids was 51 %. There

was no significant difference in histologic response between fluticasone and budesonide (48 vs. 56 %, $p = 0.632$; Fig. 1). Children and adults had a similar response to treatment (68 vs. 44 %, $p = 0.111$), and there was no significant difference in response between males and females (47 vs. 73 %, $p = 0.191$). There was no significant difference in response rates between fibrostenotic and inflammatory EoE (46 vs. 59 %, $p = 0.338$). Of the 59 patients who had documentation of clinical response, the overall symptom response rate was 71 % (42/59). No significant difference was seen between patients treated with fluticasone and budesonide (64 vs. 83 %, $p = 0.150$). To determine whether dilation influenced clinical response, we performed a Mantel–Haenszel test and found that clinical response was similar between the two treatments regardless of whether dilation was performed or not ($p = 0.224$).

There was a significant association between clinical and histologic response ($p = 0.013$). Histologic response was noted in 61 % of patients with a clinical response, while 80 % of patients without clinical response did not have histologic response.

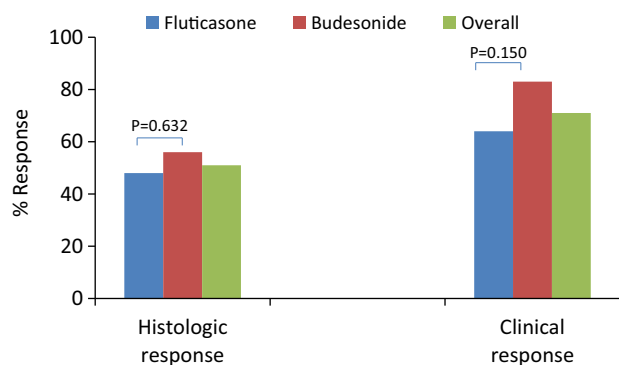
Regarding pre-treatment clinical symptoms, responders and non-responders were similar in presentation of food impaction (26 vs. 32 %, $p = 0.618$), dysphagia (82 vs. 92 %, $p = 0.309$), and heartburn (26 vs. 22 %, $p = 0.788$). In children, no significant difference was seen in clinical symptoms between responders and non-responders in abdominal pain (27 vs. 17 %, $p = 1.000$), regurgitation (40 vs. 33 %, $p = 1.000$), and vomiting (40 vs. 33 %, $p = 1.000$). Responders and non-responders had similar endoscopic features at baseline: furrows (74 vs. 84 %, $p = 0.399$), rings (50 vs. 70 %, $p = 0.100$), white plaques (24 vs. 38 %, $p = 0.217$), and strictures (19 vs. 6 %, $p = 0.203$). A similar number of responders and non-responders underwent pre-treatment dilation (26 vs. 41 %, $p = 0.226$). Peak proximal (49 ± 47 vs. 55 ± 50 , $p = 0.631$) and distal eosinophil (76 ± 85 vs. 80 ± 84 , $p = 0.852$) counts at index endoscopy were similar between responders and non-responders. Following treatment, responders had significantly less peak proximal (4.0 ± 4.4 vs. 46 ± 53 , $p < 0.001$) and distal eosinophil counts (3.5 ± 3.8 vs. 60 ± 47 , $p < 0.001$) compared to non-responders (Table 2). Using an ROC curve, we were unable to quantify any eosinophil count that would predict clinical response (area under curve of 0.387). There were no predictors to treatment response identified.

Discussion

The two commonly available topical steroid formulations for the management of EoE include fluticasone and budesonide. Both are borrowed from treatment of

Table 1 Baseline patient characteristics

	Children (<i>n</i> = 19)	Adults (<i>n</i> = 56)	<i>p</i> value
Demographics, <i>n</i> (%)			
Age (years)	9.7 ± 5.4	38.6 ± 11.5	0.001
Gender (% male)	15 (79 %)	49 (88 %)	0.454
Race (% Caucasian)	14 (74 %)	44 (79 %)	0.145
Clinical presentation, <i>n</i> (%)			
Food impaction	2 (11 %)	20 (36 %)	0.044
Dysphagia	11 (58 %)	54 (96 %)	0.001
Heartburn	1 (5 %)	17 (30 %)	0.031
Atopic history			
Asthma	10 (53 %)	5 (9 %)	0.002
Food allergy	6 (32 %)	13 (23 %)	0.545
Eczema	6 (32 %)	5 (9 %)	0.025
Allergic rhinitis	12 (63 %)	21 (38 %)	0.064
Pediatric symptoms, <i>n</i> (%)			
Abdominal pain	3 (16 %)	NA	
Regurgitation	8 (42 %)	NA	
Vomiting	7 (37 %)	NA	
Endoscopic findings, <i>n</i> (%)			
Concentric rings	3 (16 %)	42 (75 %)	0.001
Longitudinal furrows	15 (79 %)	44 (79 %)	1.000
White plaques	11 (58 %)	12 (21 %)	0.008
Strictures	0 (0 %)	17 (30 %)	0.004
% Dilation	0 (0 %)	25 (45 %)	0.001
Histologic findings			
Pre-treatment proximal eos. count	59.7 ± 50.6	49.2 ± 47.8	0.448
Pre-treatment distal eos. count	78.2 ± 99.3	71.7 ± 78.8	0.982
Treatment			
Fluticasone	14 (74 %)	34 (61 %)	
Budesonide	5 (26 %)	22 (39 %)	

**Fig. 1** There were no significant differences in histologic and clinical response between fluticasone and budesonide

pulmonary disorders, as no Food and Drug Administration (FDA)-approved treatments for EoE currently exist. There are no controlled trials to date comparing the efficacy of swallowed aerosolized fluticasone to viscous budesonide. In our retrospective study, we observed a similar response

between the two topical steroids in the treatment of EoE. We did not find any demographic, clinical, or endoscopic predictors of non-response to steroids.

For both topical steroids, response to treatment was modest, but consistent with results from several other randomized studies [6–9, 14]. One explanation for a low histologic response observed in our study may be from subtherapeutic doses of steroids. Specifically, fluticasone was not used at the current maximum recommended dose [1]. There are two studies to date which have utilized a higher dose of fluticasone and had better response to treatment [6, 9]. Alexander et al. found 62 % of adult EoE patients treated with 1760 mcg of fluticasone achieved response, defined as a 90 % decrease in post-treatment eosinophilia [6]. Similarly, in a study by Butz et al., 62 % of patients treated with 1760 mcg of fluticasone demonstrated histologic response [9]. That studies using lower doses had 50 % response at best suggests response is dose dependent [7, 8]. Interestingly, the study by Butz et al. also

Table 2 Comparison of clinical, endoscopic, and histologic features between responders and nonresponders

	Responders (<i>n</i> = 38)	Non-responders (<i>n</i> = 37)	<i>p</i> value
Demographics, <i>n</i> (%)			
Age (years)	29 ± 18	32 ± 15	0.396
Gender (% male)	30 (47 %)	34 (53 %)	0.191
Race (% Caucasian)	30 (79 %)	34 (92 %)	0.299
Clinical presentation, <i>n</i> (%)			
Food impaction	10 (26 %)	12 (32 %)	0.618
Dysphagia	31 (82 %)	34 (92 %)	0.309
Heartburn	10 (26 %)	8 (22 %)	0.788
Pediatric symptoms, <i>n</i> (%)			
Abdominal pain	4/15 (27 %)	1/6 (17 %)	1.000
Regurgitation	6/15 (40 %)	2/6 (33 %)	1.000
Vomiting	6/15 (40 %)	2/6 (33 %)	1.000
Endoscopic findings, <i>n</i> (%)			
Concentric rings	19 (50 %)	26 (70 %)	0.100
Longitudinal furrows	28 (74 %)	31 (84 %)	0.399
White plaques	9 (24 %)	14 (38 %)	0.217
Strictures	9 (24 %)	8 (22 %)	1.000
% Dilation	10 (26 %)	15 (41 %)	0.226
Histologic findings			
Pre-treatment proximal eos. count	49 ± 47	55 ± 50	0.631
Pre-treatment distal eos. count	76 ± 85	79 ± 84	0.852

suggested that non-responders to treatment have evidence of steroid resistance based on molecular gene expression [9]. EoE patients who did not achieve clinical remission demonstrated partial reversal of the pathogenic gene expression inferring steroid resistance was the reason rather than non-adherence to treatment. Therefore, if an EoE patient does not respond to a topical steroid, an alternative form of treatment such as specialized diets may be preferred over switching to another steroid.

Given the suboptimal response to topical steroids for EoE in the literature, knowledge of predictors of response may help guide patient counseling in choosing initial therapy either by increasing the dose of topical steroids or by shifting focus to alternative treatment options, such as specialized diets. While demographic factors, particularly age, may correlate with either an inflammatory or fibrostenotic phenotype of EoE, it remains unclear whether age, gender, or race influence treatment outcomes [15]. Similarly, the effect of clinical and endoscopic features on treatment outcome is unknown and largely based on anecdotal evidence.

Some studies examining predictors of response to treatment have yielded mixed results. In one such study, children with EoE with more severe inflammation at baseline had a higher response to fluticasone [16]. In another study, ambulatory pH monitoring was not reliable in predicting response to treatment [17]. In a study by Wolf et al., which had a similar rate of histologic response

(57 %) to our study, baseline dilation was found to be a predictor of non-response to steroids [18]. We did not observe a significant difference in rates of dilations between responders and non-responders to treatment. One explanation could be from a type II error, in which our sample size may not have been large enough to detect a significant difference between responders and non-responders.

Our study has some limitations. First, it was a retrospective review of a registry at a single institution which relied on accurate documentation. This limited our ability to effectively review other clinical factors, to include adherence to treatment. Although there was uniformity in the doses of steroids used, the maximum recommended dose of fluticasone was not used, potentially reducing our overall response rates. The doses were based on previous studies prior to the publication of the most recent consensus guidelines [1]. It is important to recognize, however, that higher doses of topical steroids may not be used in community practices due to cost. Another limitation was that the vehicle to create the budesonide slurry was not consistent among all patients. It remains unclear whether the use of honey versus a sugar substitute may affect mucosal contact time and therefore efficacy. Our sample size was small, making it challenging to conclude that no difference occurred between variables with a borderline *p* value. It is possible that with a larger sample the effect may have been significant. Finally, no consensus exists on

what eosinophil count constitutes a histologic response, therefore making generalized comparisons difficult to achieve.

There are also several strengths to our study. Our inclusion criteria were strict, and all patients underwent upper endoscopy before and after 8 weeks of treatment. Our cohort consisted of both children and adults. As histologic response was our primary outcome, all of our biopsy slides were re-read by a single gastrointestinal pathologist blinded to treatment.

In conclusion, fluticasone and budesonide were efficacious in inducing a histologic response in approximately half the cohort and in improving clinical symptoms in more than two-thirds of EoE patients. No predictors of steroid response could be identified. Future studies are needed to determine the reasons some EoE patients respond to steroid treatment, while others do not.

Author contributions Dustin M. Albert, Theresa A. Heifert, Steve B. Min, and Fouad J. Moawad substantially contributed to conception and design, acquisition of data, analysis and interpretation of data; drafted the article or revised it critically for important intellectual content; and approved the final version to be published. Corinne L. Maydonovitch and Thomas P. Baker analyzed and interpreted the data; drafted the article or revised it critically for important intellectual content; and approved the final version to be published. Yen-Ju Chen acquired the data, drafted the article or revised it critically for important intellectual content, and approved the final version to be published.

Compliance with ethical standards

Conflict of interest None.

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