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Effect of Proton Pump Inhibitor Treatment in "PPI Non-responsive" Patients with Eosinophilic Esophagitis

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ABSTRACT

Background & Aims: Some eosinophilic esophagitis (EoE) patients can have a decline in eosinophil count after proton pump inhibitor (PPI) treatment without achieving histologic response, but little is known about this group. We aimed to determine the effect of PPIs on reducing esophageal eosinophilia in patients deemed non-responsive to PPI therapy.

Methods: We analyzed prospectively collected cohort data from newly diagnosed adults with EoE who were histologic non-responders (≥15 eos/hpf) to PPI-only therapy. Symptoms, endoscopic histologic features were assessed before and after PPI. Pre- and post-PPI treatment esophageal biopsies were read by pathologists to determine peak eosinophil counts and other histologic findings.

Results: Of 125 patients, peak eosinophil counts were 102.1 ± 69.8 and 102.9 ± 101.1 (p=0.93) before and after PPI treatment, respectively, but lamina propria fibrosis decreased from 97% to 41% (p<0.001). Heartburn frequency also decreased (19% to 11%; p=0.006), though endoscopic findings did not change. There were 75 patients (60%) who had some decrease in eosinophil counts, with 30 patients (24%) having ≥50% decrease in counts. When comparing the ≥50% and <50% decrease groups, differences in endoscopic features were identified, but the ≥50% group had improvement in eosinophil degranulation, microabscesses, spongiosis, and basal cell hyperplasia.

Conclusion: Peak eosinophil counts did not decrease overall after PPI treatment, but symptoms of heartburn improved. Approximately a quarter had ≥50% decrease in eosinophil counts, with associated decreases in other histologic findings. Further research may consider what role PPIs have in this subset of non-responders or in combination therapies.

Key words: eosinophilic esophagitis – proton pump inhibitor – outcomes – histology – treatment.

Abbreviations: EoE: eosinophilic esophagitis; eos/hpf: eosinophil per high-power field; EREFS: EoE Endoscopic Reference Score; HSS: histologic scoring system; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; PRO: patient-reported outcome.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a clinicopathologic entity characterized by symptoms of esophageal dysfunction in the setting of an abnormal infiltration of eosinophils within the esophageal epithelium [1, 2]. It can be clinically challenging to distinguish EoE from gastroesophageal reflux disease (GERD) due to similar symptomatology and some overlapping endoscopic and histologic findings. Because of this, a trial of proton pump inhibitor (PPI) therapy was previously utilized to distinguish the diseases, with clinicopathologic improvement suggesting GERD and non-response confirming an EoE diagnosis [3-6]. However, this conceptual framework was revisited with accumulating evidence that patients with esophageal eosinophilia and a clinical presentation consistent with EoE rather than GERD demonstrated responsiveness to PPI therapy [7]. Moreover, such patients could not be readily distinguished from PPI non-responders after examining clinical, endoscopic, molecular and histological features [8-13]. Current EoE guidelines therefore have removed the PPI trial as a diagnostic criterion and instead position PPIs as a potential first line therapy [12, 14, 15].

Multiple studies support PPI effectiveness and mechanisms as a treatment modality for EoE [13, 16, 17]. Beyond acid-suppressive effects, emerging data have shown that PPIs could reduce esophageal eosinophilia through novel mechanisms, including suppression of the Th2 cytokine-induced eotaxin-3 expression in esophageal epithelium, as well as improving esophageal epithelial barrier function and other homeostatic pathways [18-20]. Clinically, a 2016 meta-analysis found that PPIs have histologic and symptomatic response rates of 50% and 60%, respectively [17], and a 2020 multi-center study examining 630 patients found a similar efficacy profile [21]. However, when assessing "PPI response", most studies assess dichotomous histologic outcomes, primarily at the 15 eosinophil per high-power field (eos/hpf) threshold [22-24]. In these cases, the extent of any decrease in esophageal eosinophilia or other associated histologic findings is not generally considered. Therefore, the effect of PPIs on the esophageal eosinophil count in patients who were deemed "non-responders" is unknown, and it remains unclear whether PPIs may benefit in patients who do not achieve PPI-mediated histologic remission.

The present study aims to address this topic by determining the effect that PPIs have on reducing esophageal eosinophilia in patients deemed non-responsive to PPI therapy, and to assess clinical correlates of any decline in eosinophilia. We hypothesized that PPIs would be associated with a significant reduction in esophageal eosinophilia for patients who were previously deemed "non-responsive" at the 15 eos/hpf threshold.

METHODS

Study Design and Patient Population

We performed a secondary analysis of a prospective cohort study of patients with EoE, the details of which have been previously reported [10, 25-28]. In the parent study, patients with symptoms of esophageal dysfunction (e.g. dysphagia, heartburn) were enrolled prior to endoscopy at our center, and were subsequently classified as an EoE case or a non-EoE control, as per EoE diagnostic guidelines. For the current study, patients were included if they were adults (≥18 years old) who had an incident diagnosis of EoE and did not meet the threshold for histologic responsiveness (<15 eos/hpf) after PPI-only therapy (at a total daily dose of 40-80 mg of any of the approved medications, for at least 8 weeks; the follow-up endoscopy was performed after the initial 8 weeks of PPI treatment, while the patient was still taking a PPI). For study inclusion, patients also had to have both the pre-PPI and post-PPI treatment esophageal biopsies available for re-review by the study pathologists, which decreased the sample size somewhat from our previously reported largest cohort [26].

Data Collection and Outcomes

During the parent study, clinical, endoscopic, and histologic data were prospectively collected for the baseline diagnostic (pre-PPI treatment) endoscopy and for the post-treatment exam to assess response to PPI therapy. Clinical information included demographics, concomitant atopic diseases, and types of symptoms. As this cohort study was designed and conducted prior to the development of validated patient-reported outcomes (PROs) for EoE, we were not able to include measures such as these. On endoscopy, pertinent findings related to EoE were recorded, including features in the EoE Endoscopic Reference Score (EREFS; total score range 0-9, with higher scores indicating worsening endoscopic severity) [29-31], and whether esophageal dilation was performed.

During both the baseline and post-treatment endoscopy, esophageal biopsies were obtained from the distal and proximal esophagus and sent for routine processing for hematoxin and eosin staining; of note, at least 5 biopsy fragments total were obtained from each patient to maximize diagnostic sensitivity. For this study, the pre- and post-PPI esophageal biopsies were read by the study pathologist as per our previously validated protocol [32-34]. The peak eosinophil count (eos/hpf; high-power field = 0.24mm^2) was determined overall for the highest area throughout the esophagus, as well as for the distal and proximal esophageal areas. In addition, other histologic findings such as eosinophil degranulation, eosinophil microabscesses, basal zone hyperplasia, spongiosis, and lamina propria fibrosis (when subepithelial stroma was present) were assessed. As the parent study was designed prior to development of the validated EoE Histologic Scoring System (HSS) [35], this metric could not be included.

Statistical Analysis and Sample Size Considerations

Characteristics of the study population were summarized with descriptive statistics, and the symptoms, endoscopic features, and histologic findings were compared pre- and post-PPI treatment. Continuous variables, such as the peak eosinophil counts, were compared using paired t-tests, while categorical variables were compared with McNemar's test. In an additional analysis, patients with a 50% or more decrease in peak eosinophil counts were compared to those with a <50% decrease in counts. Here, continuous values were compared with two-sample t-tests and categorical variables were compared with the chi-squared test. Peak eosinophil counts were also assessed for the distal and proximal locations, and post-treatment counts were correlated with post-treatment EREFS scores. This study was approved by the UNC IRB, and patients provided consent for participation in the parent study as well as consent for future use of their collected data.

RESULTS

Baseline Patients' Characteristics

There were 125 EoE patients classified as PPI non-responsive based on pre- and post-PPI treatment histology who were included in this study. The mean age was 39.4 years, 66% were male, and 94% were white. Concomitant atopy was common, with 69% having any allergic condition, 64% with allergic rhinitis, 30% with asthma, 9% with eczema, and 27% with food allergies.

Histologic, Clinical, and Endoscopic Responses to PPI Treatments

Prior to PPI treatment, the mean overall peak eosinophil count was 102.1 ± 69.8. After treatment, this was unchanged at 102.9 ± 101.1 (p=0.93); there were also no changes overall

by proximal and distal location. For other associated histologic findings, there was a trend towards a decrease in basal cell hyperplasia after PPI treatment (73% vs. 51%; p=0.06) and lamina propria fibrosis decreased from 97% to 41% of specimens with evaluable subepithelial stroma (p<0.001); no other histologic changes were noted (Table I). For symptoms, dysphagia persisted but heartburn decreased after PPI treatment (19% vs. 11% reporting this symptom; p=0.006). Endoscopic findings related to EoE were common in this cohort and all individual findings generally persisted with PPI treatment, though the total EREFS scores decreased mildly (5.0±1.9 vs. 4.5±2.2; p=0.04) and furrows increased from before to after PPI treatment (77% vs 88%; p=0.02) (Table I).

Despite no overall change in peak eosinophil counts after PPI treatment, when examining the distribution of counts before and after treatment, there was somewhat of a shift to lower counts (Fig. 1). Moreover, examination of trends in individual patient counts showed some patients decreased while some were stable or even increased, both overall and by esophageal level (Fig. 2).

Further stratification revealed that 75 patients (60%) had some decrease in eosinophil counts, while 30 (24%) had a decrease of at least 50%. The average decrease in this group was 69.9%, representing >100 eos/hpf. When comparing the subgroups with a ≥50% and <50% decrease, few histologic or endoscopic differences were identified either at baseline or

Table I. Characteristics before and after PPI treatment for the PPI non-responsive EoE patients (n=125)

	Pre-PPI treatment	Post-PPI treatment	p*
Age at diagnosis (mean years ± SD)	39.4 ± 13.4	-	--
Male (n, %)	82 (66)	-	-
White (n, %)	118 (94)	-	-
Symptoms (n, %)			
Dysphagia	120 (96)	122 (98)	0.50
Heartburn/reflux	24 (19)	14 (11)	0.006
Abdominal pain	10 (8)	6 (5)	0.22
Nausea/vomiting	2 (2)	2 (2)	1.0
Endoscopic findings (n, %)			
Exudates	68 (55)	67 (54)	0.77
Rings	91 (73)	100 (80)	0.13
Edema	53 (43)	64 (51)	0.16
Furrows	96 (77)	110 (88)	0.02
Stricture	59 (48)	61 (49)	0.85
Narrowing	31 (25)	40 (32)	0.18
Hiatal hernia	19 (15)	21 (17)	0.83
Dilation performed	58 (46)	57 (46)	0.73
Initial diameter (mean mm ± SD)	9.9 ± 4.2	11.9 ± 3.8	<0.001
Final diameter (mean mm ± SD)	12.6 ± 3.0	13.9 ± 3.0	< 0.001
Total EREFS score (mean ± SD)†	5.0 ± 1.9	4.5 ± 2.2	0.04
Peak eosinophil count (mean eos/hpf ± SD)	102.1 ± 69.8	102.9 ± 101.1	0.93
Median eos/hpf (IQR)	80 (47-148)	75 (34-130)	0.31
Other histologic findings (n, %)‡			
Eosinophil degranulation	58 (95)	55 (90)	0.51
Eosinophil microabscesses	37 (70)	37 (70)	1.0
Basal cell hyperplasia	24 (73)	17 (51)	0.06
Spongiosis	56 (95)	53 (90)	0.51
Lamina propria fibrosis	28 (97)	12 (41)	< 0.001
Eosinophil counts by location			
Distal peak (mean eos/hpf ± SD)	99.1 ± 66.6	84.2 ± 106.8	0.20
Median (IQR)	74 (47-145)	56 (23-103)	
Proximal peak (mean eos/hpf ± SD)	67.3 ± 69.6	63.5 ± 80.0	0.71
Median (IQR)	45 (18-95)	29 (5-94)	

* Means compared with a paired t-test and proportions compared with McNemar's test; † Paired EREFS data available for n=52; ‡ Paired other histology data available for n=61, n=53, n=33, n=59, and n=29 for degranulation, microabscesses, basal cell hyperplasia, spongiosis, and lamina propria fibrosis (of 56 patients with stroma present), respectively. SD: standard deviation; eos/hpf: eosinophil per high-power field; EREFS: Eosinophilic Esophagitis Endoscopic Reference Score; IOR: interquartile range.

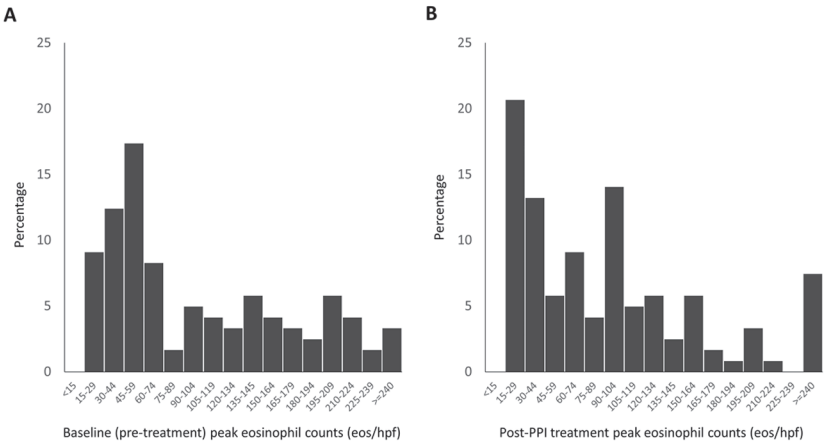

Fig. 1. Distribution of peak eosinophil counts before (A) and after (B) PPI treatment in patients who did not respond to PPI treatment.

post treatment (Table II). One exception, however, was that the baseline (pre-treatment) peak eosinophil count was nearly twice as high in the ≥50% decrease group (160.2±71.5 vs. 83.7±58.6; p<0.001). In addition, those with a ≥50% decrease had post-treatment improvement in eosinophil degranulation (67% vs. 95%; p=0.004), microabscesses (25% vs. 70%; p=0.01), basal cell hyperplasia (14% vs. 57%; p=0.03) and spongiosis (60% vs. 92%; p=0.005) compared to the <50% group. Although the post-treatment EREFS did not vary between the two groups, there was an overall mild correlation between the decrease in the post-treatment eosinophil count and decrease in post-treatment EREFS (Spearman's rho=0.36; p=0.002).

DISCUSSION

The role of PPIs in diagnosis and treatment of EoE has evolved over time, and PPIs are now considered a first-line therapeutic option rather than a diagnostic criterion [12, 14]. Assessment of PPI response, however, is often based on a dichotomous histologic cut-off of 15 eos/hpf which could preclude a more subtle understanding of potential treatment benefit even in so-called PPI "non-responders". To assess this question, we examined a prospective cohort of patients treated with PPI clinically for EoE but who were histologically non-responsive. We found that while the peak eosinophil counts were unchanged in this overall population, there were some signs of improvement that included a decrease in heartburn symptoms and less frequently noted basal cell hyperplasia and lamina propria fibrosis on biopsy. Moreover, about 25% of patients had at least a 50% decrease in eosinophil counts, which represented a large decrease in overall eosinophil burden (>100 eos/hpf). This decrease tracked with improvement in other histologic features of EoE, including eosinophil degranulation and microabscesses, basal cell hyperplasia, and spongiosis, compared to the patients who did not have the decrease, but was not associated with many other clinical or endoscopic features.

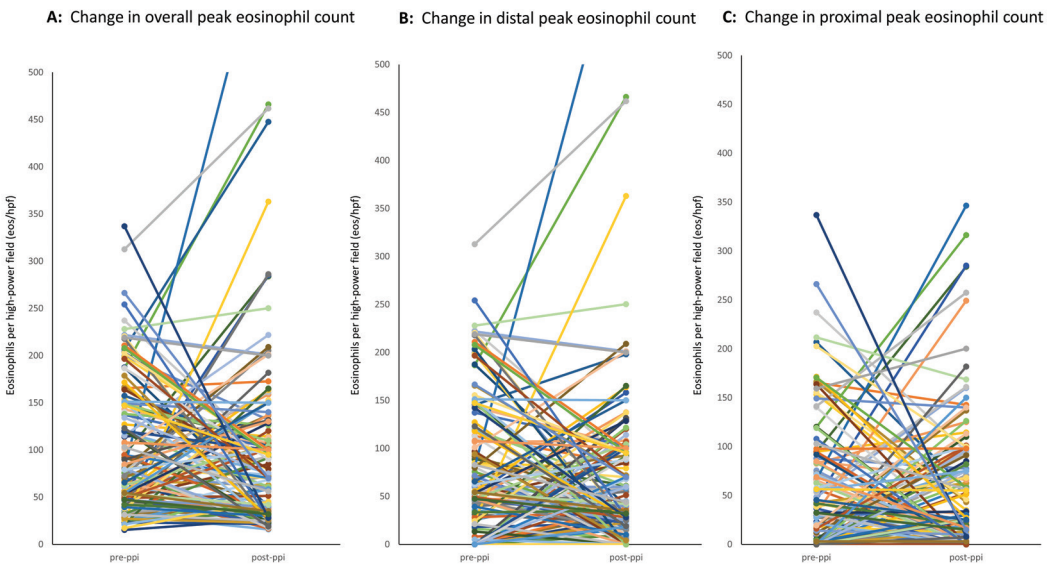

Fig. 2. Spaghetti plots for individual patient changes in eosinophil counts before and after treatment for the overall peak counts (A), distal counts (B), and proximal counts (C).

Table II. Comparison of baseline (pre-PPI treatment) and post-PPI treatment features of patients with <50% and ≥ 50% decrease in eosinophil counts after PPI treatment

	<50% decrease in eosinophil counts (n = 95)	≥ 50% decrease in eosinophil counts (n = 30)	p*
Age at diagnosis (mean years ± SD)	39.6 ± 13.2	38.6 ± 14.2	0.72
Male (n, %)	64 (67)	18 (60)	0.46
White (n, %)	90 (95)	28 (93)	0.77
Symptoms (n, %)			
Dysphagia	92 (97)	28 (93)	0.39
Heartburn	18 (19)	6 (20)	0.90
Abdominal pain	7 (7)	3 (10)	0.64
Nausea/vomiting	2 (2)	0 (0)	0.42
Any atopic condition (n, %)	49 (68)	10 (71)	0.80
Baseline peak eosinophil counts (Mean eos/hpf ± SD)			
Overall	83.7 ± 58.6	160.2 ± 71.5	< 0.001
Distal	83.7 ± 61.1	130.2 ± 70.4	0.001
Proximal	54.7 ± 51.0	104.0 ± 91.0	0.001
Post-PPI treatment peak eosinophil counts (Mean eos/hpf ± SD)			
Overall count	120.7 ± 108.9	46.5 ± 30.8	< 0.001
Overall percent decrease (mean ± SD)	81.1 ± 198.2	-69.9 ± 14.0	< 0.001
Distal count	92.4 ± 106.2	40.6 ± 31.5	0.01
Proximal count	70.2 ± 79.1	23.2 ± 31.1	0.003
Baseline endoscopic findings (n,%)			
Exudates	50 (54)	18 (60)	0.55
Rings	69 (74)	22 (73)	0.93
Edema	34 (37)	19 (63)	0.01
Furrows	70 (75)	26 (87)	0.19
Stricture	45 (50)	14 (47)	0.83
Narrowing	20 (22)	11 (37)	0.10
Hiatal hernia	16 (17)	3 (10)	0.34
Dilation performed	45 (50)	13 (43)	0.53
Initial diameter (mean mm ± SD)	10.7 ± 4.0	8.7 ± 3.0	0.16
Final diameter (mean mm ± SD)	13.4 ± 3.7	13.4 ± 3.7	0.98
Total EREFS score (mean ± SD)†	4.9 ± 2.1	5.5 ± 1.4	0.36
Post-treatment endoscopic findings (n, %)			
Exudates	55 (58)	12 (40)	0.09
Rings	77 (81)	23 (77)	0.60
Edema	50 (53)	14 (47)	0.57
Furrows	86 (91)	24 (80)	0.12
Stricture	46 (48)	15 (50)	0.88
Narrowing	32 (34)	8 (27)	0.47
Hiatal hernia	17 (18)	4 (13)	0.56
Dilation performed	45 (47)	12 (40)	0.48
Initial diameter (mean mm ± SD)	11.9 ± 4.4	11.7 ± 3.6	0.88
Final diameter (mean mm ± SD)	14.5 ± 3.1	13.8 ± 2.6	0.50
Total EREFS score (mean ± SD) †	4.0 ± 1.9	3.7 ± 2.7	0.58
Baseline other histologic findings (n, %)‡			
Eosinophil degranulation	83 (94)	23 (100)	0.24
Eosinophil microabscesses	55 (71)	16 (70)	0.93
Basal cell hyperplasia	41 (85)	8 (80)	0.67

Table II (continued)			
Spongiosis	83 (98)	22 (96)	0.61
Lamina propria fibrosis	50 (98)	12 (92)	0.29
Post-treatment histologic findings (n, %)‡			
Eosinophil degranulation	58 (95)	6 (67)	0.004
Eosinophil microabscesses	43 (70)	2 (25)	0.01
Basal cell hyperplasia	34 (57)	1 (14)	0.03
Spongiosis	56 (92)	6 (60)	0.005
Lamina propria fibrosis	14 (38)	3 (60)	0.34

* Means compared with a two-sample t-test and proportions compared with chi-square; # Data available for n=72 and n=14, respectively; † EREFS data available for n=54 pre-treatment and n=99 post-treatment; ‡ Other histology data available for n=111, n=101, n=58, n=108, and n=64 for degranulation, microabscesses, basal cell hyperplasia, spongiosis, and lamina propria fibrosis (of 102 patients with stroma present), respectively at baseline, and for 70, 69, 67, 71, and 48 (of 68 patients with stroma) after PPI treatment. For the rest of abbreviations see Table I.

Nevertheless, our findings raise the question of whether there is a subgroup of EoE patients who may benefit from ongoing PPI treatment even in the absence of a formal histologic response.

Because EoE patients who are non-responders to PPIs are subsequently placed on different treatments as recommended in guidelines and treatment algorithms [14, 36-38], there are limited data as to the characteristics and outcomes from PPI treatment alone in this group. A recent meta-analysis presented in abstract form identified 10 prior studies reporting some data on post-PPI eosinophil counts in a total of 289 non-responsive patients [39]. It found that post-PPI eosinophil counts increased slightly (from 55.7 to 66.6 eos/hpf) in the non-responsive group though heterogeneity for the pooled analysis was high (I^2=94.5%). These data are consistent with our overall findings, though this meta-analysis was not able to assess if a sub-group may have benefited, as the studies assessed therein also did not perform this analysis. In a study by Molina-Infante et al. [7], the change in eosinophil counts before and after treatment is presented for individual patients and there are a number of patients with improved counts who do not meet a strict response threshold, but again this subset is not specifically analyzed. Similarly, in a large study of PPI use in the EoE CONNECT Registry by Laserna-Mendieta et al. [21], the non-responders are identified but post-PPI counts and clinical correlates are not specifically assessed in this group. We also did not see esophageal location-specific differences with PPI treatment, whereas a prior study by Park et al. [21] suggested that the proximal esophagus had a more prominent treatment effect with PPIs.

Our data suggest that there could be a role of ongoing PPI use in EoE patients, even in those without a traditional histological response. First, there could be an impact on symptom improvement. While we did not see a change in reports of dysphagia, we did see a decrease in heartburn. This would be consistent with findings from a prior study showing that a large proportion of PPI non-responders remained on PPI treatment, and the reason in more than a quarter was because of perceived symptom improvement [40]. It is possible this is because of treatment of concomitant GERD with EoE, but our present study design does not allow us to investigate this. We also detected signs of histologic improvements beyond just the eosinophil counts and associated findings related to eosinophils (e.g. degranulation and microabscesses) in some patients. PPIs was previously shown to improve esophageal epithelial barrier function in EoE patients as well as have a broad set of effects on epithelial homeostasis [19, 20]. To that end, we saw improvements in spongiosis (also termed dilated intercellular spaces) and basal cell hyperplasia, which, in addition to barrier function, has been implicated in esophageal remodeling and persistence of symptoms despite resolution of eosinophilia [41]. Our results related to fibrosis, however, were somewhat conflicting. We did not observe endoscopic improvement in esophageal rings, strictures, narrowing, or need for dilation after PPI treatment. This is consistent with a recent study of long-term treatment with PPIs where fibrotic changes persisted [16]. However, we also saw less lamina propria fibrosis histologically after PPI, which would be consistent with other reports [42], though we must interpret this finding with caution as less than half of our subjects had subepithelial stroma present for evaluation. Nevertheless, future studies could examine whether maintaining PPI in a subset of patients (based on our data, perhaps those with heartburn symptoms, very high baseline counts, or a decrease of at least 50% in eosinophil counts with improvement in other histologic features) or using PPIs in combination with other medications, increases treatment efficacy. While one abstract suggests that PPIs may not have this type of impact in combination with a budesonide suspension [43], the question remains largely unanswered with most available treatments.

This study has limitations. First, the patients are all adults, so our results cannot be extrapolated to the pediatric EoE population. Second, the study was conducted at a tertiary referral center, which could impact generalizability. However, because all subjects were incident cases, even though they were diagnosed at our center they were not quaternary referrals and likely reflect the characteristics of newly diagnosed adults. Third, given that the study design and initial conduct predated development of certain validated symptom metrics or histologic scores, these could not be incorporated. Although we were able to assess several non-eosinophil count histologic features to provide additional detail on the biopsy assessment, our symptom data must be interpreted with caution. A final limitation is that the PPI treatment in this study was prescribed under usual clinical care, so a single specific dosing regimen was not used. However, the doses that were used mirror usual

clinical practice. Related to this, we only have data for the initial PPI course, so longer-term data would still be needed, and we are not able to perform sub-analyses by PPI type or exact dosing, and this could be a focus of future research. There are also multiple strengths to this study. It was a prospective cohort of incident EoE cases who were treatment naïve at baseline with comprehensive patient characterization and data collection, and biopsies were reviewed specifically by the study pathologists, so all pre-post comparisons were done with counts quantified using identical and validated methods, rather than relying on counts that were reported for clinical purposes in the medical record.

CONCLUSIONS

This prospective cohort study found that the peak eosinophil counts did not improve overall after PPI treatment in EoE patients who were previously deemed non-responsive at the 15 eos/hpf threshold. However, symptoms of heartburn improved and a subgroup of approximately one quarter of patients had at least a 50% decrease in eosinophil counts, corresponding to a count decrease of >100 eos/hpf, and with associated decreases in other histologic findings related to barrier function and proliferation/remodelling compared to those without a decrease. In contrast, endoscopic findings and most other symptoms did not significantly change after PPI treatment. Further research may consider what role, if any, PPIs have in subsets of "non-responders" or as combination therapies, and whether a binary histologic response assessment is appropriate in all cases.

Conflicts of interest: E.S.D. is a consultant for Abbott, Abbvie, Adare/Ellodi, Aimmune, Akesobio, Alfasigma, ALK, Allakos, Amgen, Arena, Aslan, AstraZeneca, Avir, Biorasi, Calypso, Celgene/Receptos/BMS, Celldex, Eli Lilly, EsoCap, Eupraxia, Ferring, GSK, Gossamer Bio, Holoclara, Invea, Landos, LucidDx, Morphic, Nextstone Immunology, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Salix, Sanofi, Shire/Takeda, Target RWE, Upstream Bio, receives research funding from Adare/Ellodi, Allakos, Arena, AstraZeneca, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Shire/Takeda, and has received an educational grant from Allakos, Banner, and Holoclara. None of the other authors report and potential conflicts of interest with this study.

Authors' contribution: K.P.T designed the study, collected and interpreted the data, drafted the manuscript and revised it. H.P. conceived and designed the study, interpreted the data and revised the manuscript. S.L., M.F., S.K., A.I. collected data, interpreted the results, and revised the manuscript. E.S.D conceived and designed the study, collected, and analyzed the data, interpreted the results, drafted the manuscript and revised it critically. All the authors approved the final version of the manuscript.

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