Effect of proton pump inhibitor treatment in “PPI non-responsive” patients with eosinophilic esophagitis

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Introduction

- Proton pump inhibitors (PPIs) are now a first-line treatment option for eosinophilic esophagitis (EoE), but historically patients were divided into PPI responders and non-responders for diagnosis of EoE.
- Some EoE patients can also have a decline in eosinophil count after a PPI trial without achieving a histologic response threshold, but little is known about this group of patients.
- We aimed to determine 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.

Methods

- **Study design**: Secondary analysis of a prospective cohort study from the University of North Carolina Hospitals (UNC) EoE Clinicopathologic database
- **Cases**: Adult patients who had an incident diagnosis of EoE after upper endoscopy at UNC but did not meet the threshold for histologic response (<15 eos/hpf) after PPI-only therapy (at a total daily dose of 40-80mg, of any of the approved medications, for at least 8 weeks).
- **Data**: We extracted clinical symptoms, endoscopic features, and histologic features of esophageal biopsy samples.
- Pre- and post-PPI treatment esophageal biopsies were read by pathologists to determine peak eosinophil counts and other histologic findings.
- We compared eosinophil counts and other measures of response between these groups.

Results

- We identified 125 EoE patients previously deemed PPI non-responsive with pre- and post-PPI samples available (mean age 39' 66% male; 94% white).
- In pre-PPI and post-PPI treatment groups, peak eosinophil counts averaged 102.1 ± 69.8 and 102.9 ± 101.1 (p=0.93) (Table 1).

Table 1: Characteristics before/after PPI treatment

	Pre-PPI treatment	Post-PPI treatment	p*
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
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
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
Proximal peak (mean eos/hpf ± SD)	67.0 ± 69.6	63.5 ± 80.0	0.71

* 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

Table 2: Comparison of pre- and post-PPI features of patients with patients with <50% and ≥ 50% decrease in eosinophil counts

	<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
Baseline peak eosinophil counts			
Mean eos/hpf ± SD)	83.7 ± 58.6	160.2 ± 71.5	< 0.001
Post-PPI treatment peak eosinophil counts			
Mean eos/hpf ± SD)	120.7 ± 108.9	46.5 ± 30.8	< 0.001
Percent decrease (mean ± SD)	81.1 ± 198.2	-69.9 ± 14.0	< 0.001
Post-treatment endoscopy 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
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
† 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

- With the exception of a decrease in heartburn (19% vs 11%; p=0.006), symptoms were similar pre/post treatment, as were endoscopic findings (Table 1).
- Further stratification revealed that 75 patients (60%) had some decrease in eosinophil counts, with 30 patients (24%) having a ≥50% decrease in counts (Table 2).
- In ≥ 50% decrease and <50% decrease groups, no statistically significant histologic or endoscopic changes were identified, but the ≥50% decrease group had improvement in eosinophil degranulation, microabscesses, and spongiosis, consistent with decreased eosinophil counts (Table 2).

Conclusions

- Peak eosinophil counts and symptoms of dysphagia did not change overall after PPI treatment in EoE patients deemed non-responsive, but frequency of heartburn improved.
- Approximately a quarter of EoE patients had ≥50% decrease in eosinophil counts, reflecting a >100 eos/hpf decrease, which was associated with improvements in other histologic findings; however, endoscopic and symptomatic findings did not significantly vary.
- The effect of PPIs in “non-responders”, and whether PPIs have a role in combination therapies in this sub-group, should be prospectively studied.

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