Proton pump inhibitor responsive esophageal eosinophilia, a distinct disease entity?

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Abstract
Recent studies have suggested the existence of a patient population with esophageal eosinophilia that responds to proton pump inhibitor therapy. These patients are being referred to as having proton pump inhibitor responsive esophageal eosinophilia (PPI-REE), which is currently classified as a distinct and separate disease entity from both gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE). The therapeutic effect of proton pump inhibitor (PPI) on PPI-REE is thought to act directly at the level of the esophageal mucosa with an anti-inflammatory capacity, and completely independent of gastric acid suppression. The purpose of this manuscript is to review the mechanistic data of the proposed immune modulation/anti-inflammatory role of PPI at the esophageal mucosa, and the existence of PPI-REE as a distinct disease entity from GERD and EoE.

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Key words: Gastroesophageal reflux disease; Eosinophilic esophagitis; Proton pump inhibitor responsive esophageal eosinophilia; Proton pump inhibitor

Core tip: The concept of pump inhibitor responsive esophageal eosinophilia (PPI-REE) is relatively new. The underlying mechanism(s) of PPI-REE pathogenesis and therapeutic effect of the PPI are still unknown. It is currently still unclear if PPI-REE is a subtype of gastroesophageal reflux disease (GERD), an eosinophilic esophagitis (EoE) phenotype, or a distinct entity. The aim of this manuscript is to review the mechanistic data of the proposed immune modulation/anti-inflammatory role of PPI at the esophageal mucosa, and the existence of PPI-REE as a distinct disease entity from GERD and EoE.
EoE is a primary disorder of the esophagus, first described in 1978[8], and recognized clinically in 1995[9]. An epidemiological report released in 2013 showed that EoE may affect over 400000 people in the United States[9]. Originally thought as primarily a disease of childhood, recent data suggest otherwise; the vast majority of EoE diagnoses are within adults[9]. However, the clinical presentation seems to vary by age. Young children are more likely to present with non-specific upper gastrointestinal symptoms, failure to thrive, and abdominal pain[10], while older children more commonly present with food impaction or dysphagia[11]. Adults may present with similar symptoms, however, the diagnosis is typically made in young males with history of allergy who present with food impaction and dysphagia[11,12]. Interestingly, over 50% of patients with EoE may have associated atopic disease, most commonly asthma (23%) or rhinitis (42%)[10], and this is often used as an indication the patient truly has EoE rather than GERD. However, it should be noted that asthma is actually much more common in patients with GERD, with approximately 60% of patients suffering from asthma[13]. Additionally, allergic rhinitis has been reported at greater than 40% in the general population, making the association with EoE of little value[14]. Although the etiology remains unknown, allergy remains the most likely possibility. Indeed, several studies have implicated food allergy and aeroallergens as plausible etiologic agents[15-18].

EoE is challenging to diagnose in that it requires an integrative approach, including clinical and pathologic correlation, to correctly differentiate this entity from its most common differential diagnosis-GERD. Unfortunately, clinical symptoms are often non-specific, and therefore do not aid in distinguishing a primary esophageal eosinophilic inflammatory process from acid mediated disease[9]. Endoscopic findings, if present, generally consist of esophageal concentric rings, linear furrowing, and white plaques; although these findings currently do not assist in distinguishing GERD from EoE[11,19]. Thus, the initial step in differentiating GERD from EoE begins with esophageal biopsy[9]. Greater than 15 eosinophils per high-power field (hpf) should be present in at least one field to support the diagnosis of EoE. GERD, on the other hand, is thought to contain a minor eosinophilic component, usually limited to less than 7 eosinophils/hpf and restricted to the distal esophagus[20-22]. Unfortunately, this “less-than-7” criterion is largely untested, and given that GERD is much more prevalent than EoE, even the rare occurrence of more than 15 eosinophils/hpf diminishes the predictive value of this histologic finding in differentiating these two diseases[9]. Also, the evaluation of maximal eosinophil count may provide no distinction between GERD and EoE[9]. Apart from eosinophil count, other major and minor histopathologic features may aid in the diagnosis of EoE. Major histopathologic criteria, such as degranulation of eosinophils, superficial layering of eosinophils, and eosinophilic microabscesses, defined as foci of at least four clustered eosinophils, and minor features such as lamina propria fibrosis, the presence of eosinophils in a fibrotic lamina propria (at least 5/hpf), and basal zone hyperplasia[21]. Concomitant with histological evaluation, GERD should also be ruled out by conventional diagnostic tests, such as pH monitoring; there must be a lack of clinical or histologic response after two months of PPI therapy to definitively diagnose EoE[10]. In short, the diagnosis of EoE rests on the identification of an esophageal eosinophilic infiltrate that demonstrates normal pH monitoring and persists despite PPI therapy.

Currently, there are two generally acceptable treatment modalities for EoE in both children and adults - corticosteroid therapy and dietary modification[20,24]. In children, EoE responds favorably to specific food protein elimination or elemental diets, in keeping with the proposed etiologic role of food allergy[10]. In adults, however, treatment with swallowed corticosteroid aerosols is generally more reliable than dietary intervention[16]. Nonetheless, recent literature indicates that PPIs may be involved in the treatment of esophageal eosinophilia. The identification of a patient population that exhibits esophageal eosinophilia, does not appear to have GERD, and yet seem to respond to PPI therapy, supports these reports[22,23]. This patient population is recently being referred to as having a “proton pump inhibitor responsive esophageal eosinophilia” (PPI-REE)[20,26]. PPI-REE is currently not considered as an EoE phenotype, nor is it considered as a subtype of GERD[26]. What then is PPI-REE? Is it a distinct entity besides GERD and EoE?

**DIAGNOSIS OF PPI-REE**

Clinical symptoms such as heartburn, dysphagia, difficulty feeding, and foreign body impaction, may warrant an esophageal biopsy, which may in turn reveal esophageal eosinophilia. The patient should be assessed for all possible causes of esophageal eosinophilia at this time[20]. The known causes of esophageal eosinophilia are many, including GERD, EoE, celiac disease, Crohn’s disease, infection, hyperesinophilic syndrome, achalasia, drug sensitivity, vasculitis, pemphigus, and connective tissue diseases[20,27]. If further evaluation reveals eosinophils restricted to the esophagus, the most common causes are either GERD, EoE, or the recently recognized PPI-REE, and an eight week trial of PPI therapy should be initiated to help distinguish between these entities[20]. If symptoms remain after eight weeks and repeat biopsy shows persistent eosinophilia characteristically above 15 eosinophils/hpf, the diagnosis becomes EoE[10]. If the eosinophilia resolves and symptoms subside on subsequent biopsy, the diagnosis becomes either GERD or PPI-REE[8]. It is at this critical juncture that the diagnostic dilemma is identified. A clear distinction between GERD, EoE and PPI-REE is currently non-existent (Table 1).

Currently, a potential immune disorder/inflammatory mechanism for PPI-REE has emerged[23,29]. Eotaxin-3, a known eosinophil chemoattractant expressed in the esophagus[26], is induced by inflammatory cytokines and
is inhibited by PPIs, such as omeprazole\(^{[11,32]}\). These data give the impression that PPIs may exert an immune modulation/anti-inflammatory effect on the esophageal mucosa and independent of acid suppression\(^{[20,21]}\). If this is the case, the distinction between GERD and PPI-REE becomes increasingly blurred. Why these two clinically indistinguishable diseases of the esophagus -GERD and PPI-REE-with two markedly different etiologies, respond to the same class of drugs via two completely different mechanisms, and at two different locations in the gastrointestinal tract? Are they really two different diseases or is PPI-REE just a subtype of GERD?

**IS PPI-REE A DISTINCT CLINICAL ENTITY OR A SUBTYPE OF GERD CLINICALLY?**

The rationale for exploring a potential anti-inflammatory mechanism for PPIs was engendered by the identification of patient populations with esophageal eosinophilic infiltrate (EEI), that do not appear to have GERD, and that seem to respond to PPI therapy. In the study by Molina-Infante et al\(^{[33]}\), 35 patients with > 15 eosinophils/hpf were evaluated for PPI response. Of the 35 patients, 14 patients showed endoscopic findings consistent with GERD, while 15 patients demonstrated abnormal pH monitoring. Thus, a total of 29/35 patients had evidence of underlying peptic acid disease. Of the remaining 6 patients, only two showed a response to PPI therapy. Therefore, these two patients showed a unique pattern of clinical and pathologic findings. Yet three crucial and controversial issues remain unresolved. First, normal pH monitoring is not enough to exclude GERD in patients with EEI\(^{[22,34]}\). Second, > 15 eosinophils/hpf cannot reliably differentiate between GERD and a primary esophageal eosinophilia\(^{[5,28]}\). Finally, it is not surprised that GERD would be responsive to PPI therapy. It remains unclear if this study and similar studies are actually describing different disease processes when they differentiate GERD from PPI-REE, or if they are simply describing variable findings of GERD. Interestingly, in a recent review of ten relevant studies involving patients with PPI-REE, only three of the studies included pH monitoring data on their patients\(^{[35]}\). Of the three studies including pH monitoring data, one study found 100% of patients to have an abnormal pH monitoring test, which is considered diagnostic of GERD. Of the ten studies combined, only 7 of 258 (2%) patients showed the unique finding of a normal pH monitoring test with a high percentage of eosinophils on biopsy. This highlights an important issue because the pH monitoring test is not 100% sensitive, and a normal pH monitoring test does not exclude a diagnosis of GERD.

Another commonly cited study that demonstrated a patient population with EoE responsive to PPI therapy suffered from the same methodological limitations as previously described\(^{[5]}\). In this study, PPI therapy was used to categorize 36 patients with suspected EoE into the subcategories non-eosinophilic esophagitis (GERD) and EoE, with a response to therapy assessed histologically. Again, this classification scheme may still not reflect a valid distinction between GERD and EoE given the lack of pH monitoring to help further delineate which patients may have had GERD. Regardless, 14/36 patients initially responded to PPI and were classified as GERD. The remaining 22 patients were unfortunately treated with both high dose PPI and fluticasone, nullifying any possible interpretation of a selective response to PPI therapy in the remaining cohort of patients. Finally, a case series of three pediatric patients with esophageal eosinophilia responsive to PPI treatment is commonly cited as evidence of a PPI-REE. In this report, one patient had an abnormal reflux index, while the other two had no pH monitoring performed\(^{[26]}\). Again, this study does not support to a potential new disease entity - PPI-REE - because GERD was present in the first patient, and it was not ruled out the other two.

In summary, the current available clinical data have not provided sufficient evidence to support that PPI-REE is a distinct clinical entity. The clinical presentation and the therapeutic efficacy of the PPI on PPI-REE suggest that PPI-REE maybe a subtype of GERD instead of a distinct entity from EoE and GERD.

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**Table 1 Clinical and pathological features of eosinophilic esophagitis, proton pump inhibitor responsive esophageal eosinophilia, and gastroesophageal reflux disease**

| EoE                  | PPI-REE            | GERD                |
|----------------------|--------------------|---------------------|
| **Clinical Presentation** | Upper GI symptoms, NS | Upper GI symptoms, NS | Upper GI symptoms, NS |
| **PPI response after 8 wk therapy** | No response (H/S) | Positive response (H/S) | Positive response (H/S) |
| **Endoscopy** | Non-specific findings | Non-specific findings | Non-specific findings |
| **Ambulatory pH testing** | Negative | Negative or unknown | Positive |
| **Histology** | > 15 Eos/hpf, OIEB | > 15 Eos/hpf, OIEB | Generally < 7, but can be > 15 Eos/hpf, OIEB |
| **Etiology** | Allergy related? | Unknown | Reflux |
| **Molecular Features** | Eotaxin 3 mRNA increased | Unknown | Eotaxin-3 mRNA increased |

GERD: Gastroesophageal reflux disease; PPI-REE: Proton pump inhibitor responsive esophageal eosinophilia; EoE: Eosinophilic esophagitis; H: Histologic; S: Symptomatic; NS: Non-specific; PORB: Persistent on repeat biopsy after PPI therapy; OIEB: On initial endoscopic biopsy.
PROPOSED MECHANISM OF PPI IN PPI-REE: ANTI-INFLAMMATORY EFFECT?

Eosinophilic esophagitis is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [25]. Studies have shown that immune/inflammatory processes and associated cytokines/chemokines/inflammatory mediators such as eotaxin, IL5, IL13, transforming growth factor-β1, fibroblast growth factor, thymic stromal lymphopoietin and others are involved in the pathogenesis of EoE [29,36-38]. Among the involved cytokines/chemokines/inflammatory mediators, eotaxin, especially eotaxin 3 has been deeply studied in the pathogenesis of EoE and esophageal eosinophilia [39-41]. Eotaxin is a known eosinophil chemoattractant that has been primarily studied in the lung and gastrointestinal tract, where it has been shown to function in homing eosinophils to these locations. Eotaxin-3 has been designated as the predominant chemoattractant for directing eosinophils to the gastrointestinal tract below the level of the esophagus, under normal conditions [42,43]. Yet, eotaxin mRNA is expressed constitutively and in abundance in the normal esophageal mucosa, and why this does not also result in eosinophil migration to this location is unclear [42].

Eotaxin has also been examined under inflammatory conditions, and is reportedly up-regulated in esophageal biopsy specimens from children with EoE [40]. Unfortunately, in this study, a definitive diagnosis of EoE had not been made before concluding the samples came from patients with EoE. In fact, EoE was based solely on histological findings, and results of pH monitoring and response to PPI therapy were either not assessed or not reported. Furthermore, biopsy specimens in this study were strictly from the distal 5 cm of the esophagus, which is problematic given the potential for overlap with GERD. Therefore, the increased eotaxin expression in this study is probably due to acid reflux damage to the esophagus. This would be in keeping with other studies that clearly demonstrate chemokine release from the esophageal squamous mucosa caused by acid mediated damage [43,45].

Furthermore, an additional study also showed that there is no significant difference of eotaxin-3 expression in esophageal squamous mucosa in patients with GERD, EoE and normal controls [41]. The ubiquitous cell membrane phospholipid released during cell damage, sphingosine-1-phosphate, potently upregulates the chemokine receptor, CCR3, known to cause the release of eotaxin and another eosinophil chemokine known as Regulated on Activation Normal T cell Expressed and Secreted (RANTES) [41]. Similarly, findings from a study involving 32 patients with GERD demonstrated elevated levels of three eosinophil chemokines in the esophageal epithelial cells of GERD patients relative to normal controls: RANTES, monocyte chemotractant protein 1 (MCP-1), and interleukin-8 (IL8) [41].

The next line of evidence to suggest an anti-inflammation role for the PPI in the esophagus comes from data demonstrating the induced expression eotaxin-3 is via Th2 cytokines IL4 and IL13, and is mediated through STAT6 [29,47-49]. This pathway is blocked by omeprazole in squamous epithelial cells derived from patients with established EoE [25,41]. The study on esophageal squamous cells performed by Cheng et al [31] failed to report pH monitoring response to PPI therapy, and methodology related to differentiating between GERD and EoE samples. Though the study by Zhang et al [32] used cells derived from patients with EoE using clinically established guidelines, they failed to use pH monitoring to definitively rule out reflux as a contributing factor. Furthermore, they were unable to demonstrate functional data demonstrating a PPI effect on eotaxin transcription. They did demonstrate reduced STAT-6 binding to the eotaxin promoter; however, this did not reduce expression of the eotaxin-3 reporter gene, though the authors proposed the possibility of chromatin remodelling that might reduce eotaxin 3 transcriptional activity. Therefore, no definitive mechanism has yet been established. Interestingly, Cheng et al [31] found no significant difference in eotaxin-3 induction by Th2 cytokines in both the EoE and GERD derived cells. These finding, in conjunction with the absence of pH monitoring and response to PPI therapy, may suggest the possibility that the cells cultured in this study were predominantly collected in a background of acid reflux. If this were the case, this would be in keeping with the previously mentioned studies of GERD induced chemokine expression.

In summary, the current available experimental data have not provided sufficient evidence to support the immune disorder/inflammatory mechanism(s) of PPI-REE similar to that of EoE and the immune modulation/anti-inflammatory effect of PPI on PPI-REE. The esophageal eosinophilia and the therapeutic effect of PPIs on PPI-REE may share similar mechanism(s) in that of GERD by gastric acid suppression, indicating PPI-REE maybe a subtype of GERD instead of a distinct entity from EoE and GERD.

CONCLUSION

The recent recognition of PPI-REE has complicated the diagnostic algorithm for EoE and GERD. PPI-REE is the term used to describe a patient with esophageal eosinophilia on biopsy that responds to PPI therapy. Though recent guidelines require the exclusion of PPI-REE with a PPI trial before a formal diagnosis of EoE can be made, it is currently still unclear if PPI-REE is a subtype of GERD, an EoE phenotype, or a distinct entity. Furthermore, the current clinical and experimental data indicating an immune modulation/anti-inflammatory role of the PPIs on the esophagus is still insufficient. The term PPI-REE may not refer to a new diagnostic entity, but maybe a subtype of GERD. Further clinical and experimental investigations are needed to classify the recently recognized PPI-REE.
conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; 116: 536-547 [PMID: 16453027 DOI: 10.1172/JCI26679]

31 Cheng E, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, Spechler SJ, Souza RF. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut* 2013; 62: 824-832 [PMID: 22580413 DOI: 10.1136/gutjnl-2012-302250]

32 Zhang X, Cheng E, Huo X, Yu C, Zhang Q, Pham TH, Wang DH, Spechler SJ, Souza RF. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One* 2012; 7: e50037 [PMID: 23185252 DOI: 10.1371/journal.pone.0050057]

33 Molina-Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic esophagitis. *Aliment Pharmacol Ther* 2013; 37: 1157-1164 [PMID: 23656497 DOI: 10.1111/apt.12332]

34 Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus–peptic or eosinophilic esophagitis? Case series of three patients with eosinophilic esophagitis. *Am J Gastroenterol* 2006; 101: 1666-1670 [PMID: 16863575 DOI: 10.1111/j.1572-0241.2006.00562.x]

35 Blanchard C, Stucke EM, Rodríguez-Jimenez B, Burwinkel K, Collins MH, Ahrens A, Alexander ES, Butz BK, Jameson SC, Kaul A, Franciosi JP, Kushner JP, Putnam PE, Abiona A, Rothenberg ME. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. *J Allergy Clin Immunol* 2011; 127: 208-217, e1-7 [PMID: 21211656 DOI: 10.1016/j.jaci.2010.10.039]

36 Weinbrand-Goichberg J, Segal I, Ovadia A, Levine A, Dalal I. Eosinophilic esophagitis: an immune-mediated esophageal disease. *Immunol Res* 2013; 56: 249-260 [PMID: 23579771 DOI: 10.1007/s12026-013-8394-y]

37 Zafra MP, Cancelleri N, Rodriguez del Río P, Ruiz-García M, Estévez L, Andregnette V, Sánchez-García S, Fiocchi C, Collantes E, Sastre J, Quirce S, Ibáñez MD, del Pozo V. Misregulation of suppressors of cytokine signaling in eosinophilic esophagitis. *J Gastroenterol* 2013; 48: 910-920 [PMID: 23229770 DOI: 10.1007/s00535-012-0723-8]

38 Me T, Wojno ED, Spechler SJ, Souza RF, Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One* 2012; 7: e50037 [PMID: 23185252 DOI: 10.1371/journal.pone.0050057]

39 Hogan SP, Mishra A, Brandt EB, Royalty MP, Pope SM, Zimmermann N, Foster FS, Rothenberg ME. A pathological function for eotaxin and eosinophils in eosinophilic gastro-intestinal inflammation. *Nat Immunol* 2001; 2: 353-360 [PMID: 11276207 DOI: 10.1038/86365]

40 Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003; 125: 1419-1427 [PMID: 14598258]

41 Bhattacharya B, Carlsen J, Sabo E, Kethu S, Meitner P, Tavares R, Jakate S, Mangray S, Aswad B, Resnick MB. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. *Hum Pathol* 2007; 38: 1744-1753 [PMID: 17906565 DOI: 10.1016/j.humpath.2007.05.008]

42 Mishra A, Hogan SP, Lee J, Foster PS, Rothenberg ME. Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 1999; 103: 1719-1727 [PMID: 10377178 DOI: 10.1172/JCI6650]

43 Tantibhaedhyangkul U, Tatevian N, Gilger MA, Major AM, Davis CM. Increased eosinophagitis regulatory T cells and eosinophil characteristics in children with eosinophilic esophagitis and gastroesophageal reflux disease. *Ann Clin Lab Sci* 2009; 39: 99-107 [PMID: 19429794]

44 Isomoto H, Wang A, Mizuta Y, Akazawa Y, Ohba K, Omagari K, Miyazaki M, Murase K, Hayashi T, Inoue K, Murata I, Kohno S. Elevated levels of chemokines in esophageal mucosa of patients with reflux esophagitis. *Am J Gastroenterol* 2003; 98: 551-556 [PMID: 12650786]

45 Ma J, Altomare A, Guarino M, Cicala M, Rieder F, Fiocchi C, Li D, Cao W, Behar J, Biancani P, Harnett KM. HCl-induced and ATP-dependent upregulation of TRPV1 receptor expression and cytokine production by human esophageal epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2012; 303: G635-G645 [PMID: 22790595 DOI: 10.1152/ajpgi.00907.2012]

46 Roviozzi F, Del Galdo F, Abbate B, Gaggi L, D’Agostino B, Antunes E, De Dominicis G, Parente L, Rossi F, Cirino G, De Palma R. Human eosinophil chemotaxis and selective in vivo recruitment by sphenogas 1-phosphate. *Proc Natl Acad Sci USA* 2004; 101: 11170-11175 [PMID: 15254297 DOI: 10.1073/pnas.0401439101]

47 Blanchard C, Durual S, Estienne M, Emami S, Vasseur S, Cuper JC. Eotaxin-3/CCL26 gene expression in intestinal epithelial cells is up-regulated by interleukin-4 and interleukin-13 via the signal transducer and activator of transcription 6. *Int J Biochem Cell Biol* 2005; 37: 2559-2573 [PMID: 16084752 DOI: 10.1016/j.biocel.2005.06.010]

48 Hebenstreit D, Luft P, Schmiedelechner A, Duschl A, Horjeis-Rowiez K, SOCS-1 and SOCS-3 inhibit IL-4 and IL-13 induced activation of Eotaxin-3/CCL26 gene expression in HEK293 cells. *Mol Immunol* 2005; 42: 295-303 [PMID: 15589317 DOI: 10.1016/j.molimm.2004.09.004]

49 Hoecj J, Wiosetschläger M. Activation of eotaxin-3/CCL26 gene expression in human dermal fibroblasts is mediated by STAT6. *J Immunol* 2001; 167: 3216-3222 [PMID: 11544308]
