Curr Treat Options Allergy (2015) 2:90–99
DOI 10.1007/s40521-015-0047-z

Food Allergy (M Fernandez-Rivas, Section Editor)

Proton Pump Inhibitor Therapy in Eosinophilic Esophagitis: Current Role and Future Perspectives

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Published online: 12 March 2015

This article is part of the Topical Collection on *Food Allergy*

Keywords Proton pump inhibitor-responsive esophageal eosinophilia · Eosinophilic esophagitis · Gastroesophageal reflux disease · Proton pump inhibitor

Abbreviations *EDP* Eosinophilic esophagitis diagnostic panel · *EoE* Eosinophilic esophagitis · *GERD* Gastroesophageal reflux disease · *IL* Interleukin · *PPI* Proton pump inhibitor · *PPI-REE* Proton pump inhibitor-responsive esophageal eosinophilia · *STAT6* Signal transducer and activator of the transcription 6

Opinion statement

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction, eosinophil-predominant inflammation, and lack of response to high-dose proton pump inhibitor (PPI) therapy. Responsiveness to PPI therapy in patients with suspected EoE has been historically assumed as evidence of gastroesophageal reflux disease (GERD), but this concept has rapidly changed over the past few years. A novel phenotype, termed PPI-responsive esophageal eosinophilia (PPI-REE), was described in 2011. PPI-REE refers to patients who appear to have EoE, but who achieve complete remission after PPI therapy. Currently, a PPI trial is mandatory before diagnosing EoE since 30–40 % of EoE patients will be eventually diagnosed with PPI-REE. Evolving evidence on PPI-REE suggests it is not simply GERD but actually a subphenotype of EoE, given the fact PPI-REE and EoE remain genetically and phenotypically indistinguishable. Instead of PPI-REE, the term PPI-responsive EoE might be more accurate to name this entity. PPI-REE might occur with either normal or pathological esophageal pH monitoring. PPI therapy can partially restore epithelial integrity and reverse allergic inflammation gene expression in PPI-REE. Whether

esophageal barrier impairment is the cause of the effect of esophageal eosinophilia and whether PPI therapy primarily targets barrier or inflammation healing in PPI-REE have not been yet elucidated. The natural history of the disease, long-term doses, and duration of PPI therapy, as well as factors influencing symptom and/or inflammation relapse remain yet unknown. The mechanism as to why among identical patients, some respond to PPI therapy (PPI-REE) while others do not (EoE), warrants further research.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Currently, it represents the second most common cause of esophageal inflammation after gastroesophageal reflux disease (GERD) and the leading cause of dysphagia and food impaction in children and young adults [1]. The first Consensus Guidelines report on EoE was published in 2007 [2], proposing the following diagnostic criteria: (1) symptoms of esophageal dysfunction mainly dysphagia/food impaction, (2) esophageal eosinophilic infiltration (>15 eos/HPF), and (3) either absence of response to proton pump inhibitor (PPI) therapy or demonstration of normal esophageal acid exposure on pH monitoring. Therefore, it was suggested that either a response to PPI therapy or increased acid exposure on pH monitoring was consistent with GERD and, therefore, ruled out EoE. The premise underlying this recommendation was that GERD, as an acid-related disorder, was the only disease that could respond to the acid-suppressing ability of PPI treatment. An illustrative example of this thinking is given in the first case report of PPI-responsive esophageal eosinophilia (PPI-REE), published in 2006, in which two children and an adult with clinical, endoscopic, and histological data suggestive of EoE, achieved complete response to PPI therapy [3]. The authors literally concluded that "while these patients presentation was highly suggestive of allergic esophagitis, their symptoms, and the gross and histologic esophageal abnormalities normalized following treatment with a PPI, implicating acid reflux as the underlying cause."

PPI-responsive esophageal eosinophilia

Initial description

In 2011, the first prospective series was published, reporting that up to 50 % of patients with an EoE phenotype (dysphagia/food impaction and >15 eos/HPF in esophageal biopsies) achieved complete remission on PPI therapy [4••]. Clinical, endoscopic, and histological findings were indistinguishable between responders and nonresponders to PPI therapy. Of note, responsiveness to PPI therapy was observed not only in a majority of patients with GERD but also in 33 % of those without evidence of GERD by endoscopy and pH monitoring.

The description of this new potential disease phenotype was acknowledged as one of the major breakthroughs in the updated guidelines for diagnosis and management of EoE published in 2011 [5•]. These guidelines identified an emerging body of literature and clinical experience describing a subset of EoE patients whose symptoms and histopathologic findings were responsive to PPI treatment and who might or might not have well-documented GERD. Additionally, several therapeutic/basic studies interestingly suggested a potential anti-inflammatory or barrier-healing role for PPI therapy in patients with suspected EoE [6].

In 2013, the first systematic review on PPI-REE [7•] highlighted PPI-REE as a prevalent entity (>30 % of patients with suspected EoE) and its growing importance in literature, especially in adult patients. PPI-REE was significantly higher in patients with documented GERD, but it occurred in almost a third of patients without GERD (70 vs. 29 %, $p<0.001$).

Prevalence

Over the past 2 years, several large adult series from the USA and Europe have corroborated 35–43 % of patients with suspected EoE that are eventually diagnosed with PPI-REE [8, 9, 10••]. As such, a PPI trial before arriving at a diagnosis of EoE is currently mandatory in order to avoid unnecessary therapeutic interventions in PPI-REE, such as topical steroids or elimination diets. Diagnostic and therapeutic implications of PPI-REE have been also included and highlighted in the recently published third (2013) and fourth (2014) iteration of clinical guidelines [11, 12]. Table 1 summarizes the rapidly evolving consideration of PPI responsiveness in patients with suspected EoE over the past 7 years.

Distinguishing features between PPI-REE and EoE

At the present time, no study has been able to demonstrate the existence of distinguishing phenotypical features between PPI-REE and EoE. Four studies have failed to find distinguishing clinical, endoscopic, and histological features at baseline between patients ultimately found to have EoE or PPI-REE after a PPI trial [4••, 9, 10••, 13]. Several studies have also confirmed the lack of usefulness of pH monitoring to predict response to PPI therapy [4••, 14–17]. Two recent studies failed to differentiate between both groups using markers of eosinophilic infiltration and associated inflammatory cells (major basic protein, eotaxin-3, and tryptase) [18] and gene expression of Th2 chemokine (eotaxin-3) and cytokines (interleukin (IL)-5 and IL-13) [10••] in esophageal biopsies.

One of the critical findings in understanding EoE pathogenesis was the discovery of the whole-genome mRNA esophageal expression profile ("EoE

Table 1. Evolving consideration of PPI responsiveness in patients with esophageal eosinophilia compatible with EoE over the past 7 years

2007 Consensus Guidelines	2011 Consensus Guidelines	2015
PPI responsiveness is equivalent to GERD	PPI responsiveness neither confirms GERD nor excludes EoE	PPI-REE might be a subphenotype of EoE
A pathological pH monitoring is equivalent to either response to PPI therapy or GERD	PPI responsiveness might occur either with normal or pathological pH monitoring	PPI-REE and EoE share both genotypical and phenotypical features
GERD, as an acid-related disorder, is the only showing response to the acid-suppressing ability of PPI therapy	PPI-REE is a new phenotype referring to patients with suspected EoE achieving complete remission on PPI therapy	PPI therapy in PPI-REE downregulates allergic inflammation in a similar way to steroids in EoE

EoE eosinophilic esophagitis, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *PPI-REE* proton pump inhibitor-responsive esophageal eosinophilia

transcriptome") [19]. More recently, a 94-gene molecular panel, termed as the EoE Diagnostic Panel (EDP), has shown 96 % sensitivity and 98 % specificity to distinguish patients with EoE in remission from controls, as well as identifying patients exposed to glucocorticoids and likely to have relapse after treatment [20]. As such, it would be interesting to ascertain whether this panel can distinguish between PPI-REE and EoE patients. A recent study has been the first to evaluate differences in EDP between untreated 28 EoE and 36 PPI-REE patients from five US centers [21••]. Of note, the gene upregulation and downregulation pattern comprising the EoE hallmark gene signature was also present in PPI-REE samples at baseline, including increased CCL26 levels for eosinophil chemotaxis, CPA3 levels for mastocytosis, IL-13 responding MUC4 levels, and POSTN levels for tissue remodeling, but not in GERD and control patients. In addition, molecular signature and mastocytosis of untreated PPI-REE were almost reversible by using PPI monotherapy in concordance with a previous recent study demonstrating that PPI therapy in PPI-REE downregulated eotaxin-3 and Th2 cytokines gene expression in esophageal tissue, similarly to that observed in EoE patients after topical steroid therapy [10••].

Updated similarities and differences between GERD, PPI-REE and EoE are summarized in Table 2.

PPI-responsive esophageal eosinophilia or PPI-responsive EoE?

Evolving evidence now shows EoE and PPI-REE are genetically and phenotypically indistinguishable; therefore, questioning whether PPI-REE and EoE are two different diseases [22]. It may be counterintuitive to define PPI-REE by its response to PPI therapy rather than by its genetic, phenotypical, and mechanistic characteristics, which are similar to those of classic EoE. We do not define

Table 2. Updated similarities and differences between GERD, PPI-REE, and EoE

	GERD	PPI-REE	EoE
Etiology	Gastric content reflux	Unknown	Food/airborne allergens
EoE genetic diagnostic panel	Not expressed	Overexpressed	Overexpressed
Symptoms	Heartburn, regurgitation, dysphagia	Dysphagia, food bolus impaction	Dysphagia, food bolus impaction
Esophageal involvement	Distal	Distal and proximal	Distal and proximal
pH esophageal monitoring	80 % increased acid exposure in erosive GERD 50 % normal acid exposure in non erosive GERD	70 % increased/30 % normal acid exposure	60 % normal/40 % increased acid exposure
Type of immune response/involved chemo/cytokines	Th1 IL-8, MCP-1, RANTES	Th2 Eotaxin-3, IL-13, IL-5	Th2 Eotaxin-3, IL-13, IL-5
Inflammatory cells	Neutrophils, lymphocytes, low-grade eosinophilia	Eosinophils and mast cells	Eosinophils and mast cells
Treatment	PPI therapy fundoplication surgery	PPI therapy	Steroids/diet

EoE eosinophilic esophagitis, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *PPI-REE* proton pump inhibitor-responsive esophageal eosinophilia

bronchial eosinophilic inflammation responsive to corticosteroids as a different entity than asthma when step-up therapy is needed. As such, it is tempting to approach EoE as a disease in which PPI therapy might be the first step in treatment and diet and steroids represent step-up therapy. Subsequently, there is a concern that the term PPI-REE might be replaced by PPI-responsive EoE.

Advances in understanding PPI-REE pathophysiology

The pathogenesis of esophageal eosinophilia in PPI-REE patients remains unknown. Furthermore, the mechanisms as to why among patients with an identical baseline genotypic and phenotypical expression, some respond to PPI therapy (PPI-REE) while others do not (EoE), are yet to be elucidated. The most well-studied effect of PPIs has been the targeted inhibition of the gastric H+/K+-ATPase in the parietal cells responsible for gastric acid secretion. Active parietal cells develop an acidic environment wherein PPIs are acid-activated. The active form of the drug then forms covalent disulfide bonds with cysteine residues on the ATPase, rendering the pumps inactive [23].

The most prevailing hypothesis to explain PPI-REE has been assuming GERD to be the priming event. Acid peptic damage to the tight junctions between epithelial cells results in increased permeability with dilation of intercellular spaces, possibly allowing the mucosal penetration of allergens that cause EoE allowing the potential entry of food-derived allergenic molecules through acid-induced epithelial barrier damage [24]. Thus, GERD-induced epithelial damage could expose the deeper layers of the esophageal squamous epithelium to antigens that ordinarily could not penetrate a normal mucosa, facilitating recognition of antigens by antigen-presenting cells to trigger a Th2 immune response in genetically predisposed patients [21••]. However, new and emerging data suggest that PPIs may benefit patients with EoE through effects that are independent of gastric acid suppression [25•]. A summary of the interplay between potential pathophysiological mechanisms and therapeutic effects of PPI therapy in PPI-REE is displayed in Fig. 1.

Restoration of epithelial barrier function of the esophageal mucosa

The first study objectively addressing this issue was published in 2014 [26••]. Sixteen patients with esophageal eosinophilia >15 eos/HPF were compared to 11 controls at baseline. Esophageal mucosal integrity was measured in the distal esophagus in vivo with a through-the-scope probe during endoscopy and in vitro with two biopsies for electron microscopic analysis of dilated intercellular spaces and four biopsies for measuring transepithelial electrical resistance and transmucosal flux of fluorescently labelled molecules sized 0.3 and 40 kDa (similar to size of food allergens) in Ussing chambers. In patients with esophageal eosinophilia, all measurements of mucosal integrity were significantly impaired when compared to controls. After PPI therapy, half of patients were categorized as PPI-REE. PPI therapy resulted in partial restoration of mucosal integrity in PPI-REE, but not in EoE patients. The authors concluded that mucosal integrity impairment in PPI-REE might be due to GERD, whereas it might be related to inflammatory cell recruitment in EoE. However, these results should be viewed with caution since acid reflux was not measured by pH monitoring and barrier healing related to potential anti-inflammatory effects of PPI therapy could not be positively ruled out.

Acid suppression

EoE patients have been recently shown to have lower thresholds for onset of symptoms and pain after esophageal acid infusion when compared to healthy volunteers [27]. As a matter of fact, EoE patients without GERD showed an earlier burning sensation than EoE patients with concomitant GERD or healthy volunteers after esophageal acid infusion [27]. Suppression of gastric acid secretion with PPIs, thus, might provide symptomatic relief even for patients with either normal or pathological esophageal acid exposure. This phenomenon, therefore, might explain why several series of EoE patients have been reported to achieve complete symptom remission on PPI therapy, despite persistent esophageal inflammation [4••, 10••, 16, 28–31]. Furthermore, a significant reduction in distal esophageal eosinophil load (not reaching the threshold below 15 eos/HPF) has been recently reported in EoE patients [10••, 32].

Anti-inflammatory effects of PPI therapy

Esophageal acid exposure in GERD can enhance the expression of adhesion molecules (e.g., vascular cell adhesion protein-1) and Th1 cytokines (e.g., IL-8 and IL-1b) and cause the release of other inflammatory mediators in the esophagus, leading to the recruitment of neutrophils, lymphocytes, and, to a lesser extent, eosinophils. In 2009, a provocative experimental study demonstrated that GERD, in contrast to classic thinking, caused esophageal inflammation through a cytokine-mediated mechanism rather than direct epithelial caustic injury [33]. In this study, the authors observed that after surgical induction of reflux, the first histologic inflammatory response detected was a lymphocytic infiltration of the submucosa which progressed to the mucosal surface. Interestingly, mucosal erosions did not appear until postoperative week 4. These findings suggest that reflux esophagitis develops primarily as an immune-related injury rather than solely as a caustic chemical injury. As such, one can speculate that in atopic patients, GERD may not induce a Th1 cytokine injury through a pathway similar to the Th2 pathway found in EoE. In this regard, a recent experimental study has shown that eotaxin-3 expression in GERD and EoE cell cultures is similar when stimulated with Th2 cytokines [34••], posing the possibility that in patients at risk for EoE, such as those with other atopic disorders, the injury of GERD may be diverted to an alternate pathway from typical erosive to EoE. More data are needed to fully assess this pathway.

Interestingly, new and emerging data suggest that PPIs may benefit patients with PPI-REE and EoE through effects that are independent of gastric acid suppression. Two recent experimental studies [34••, 35] have shown that PPIs inhibit Th2 cytokine-stimulated secretion of eotaxin-3, the primary eosinophil chemoattractant in EoE, in esophageal squamous epithelial cells. Both omeprazole and lansoprazole exhibited this inhibition, suggesting a class effect of PPIs. This inhibition occurred with omeprazole concentrations as low as 1 mmol/l, which are physiologically achievable in blood with conventional oral dosing or intravenous administration. Mechanistically, the inhibitory effect of PPIs seems to involve chromatin remodeling in the eotaxin-3 promoter, resulting in decreased promoter binding of the transcription factor protein, signal transducer, and activator of transcription (STAT)6, decreased RNA polymerase II recruitment, and, overall, reduced eotaxin-3 transcriptional activity in

esophageal squamous epithelial cells [35]. As mentioned above, these potential anti-inflammatory effects have been recently corroborated in clinical studies [10••, 21••].

Future perspectives in PPI-REE

Multiple diagnostic and therapeutic dilemmas surrounding PPI-REE are shown in Table 3. The precise etiology and mechanistic pathophysiology of PPI-REE remain unknown (Fig. 1). Another main issue is we do not understand why among identical patients, some respond to PPIs (PPI-REE) yet others do not (EoE). Following the lead of other diseases, there may be genomic differences or subtle variations in disease pathways that explain therapeutic response. In the first study evaluating the EoE diagnostic panel in PPI-REE and EoE patients, *KCNJ2* (potassium inwardly rectifying channel, subfamily J, member 2/Kir2.1) became the only gene with significant differential expression between both disorders [21••]. *KCNJ2* resulted in 72 % sensitivity and 72 % specificity to predict PPI-REE-pre versus EoE. *KCNJ2* encodes the potassium channel Kir2.1, which is abundant in gastrointestinal mucosa and colocalizes with the H1-K1-ATPase/proton pump. Therefore, the authors propose a potential interaction between this potassium channel and proton pump in the upper gastrointestinal epithelium to explain PPI-REE.

Another important unsolved issue is to ascertain whether PPI-REE and EoE also share a similar natural history and long-term management. EoE has been demonstrated to be a chronic disease with persistence of symptoms and inflammation over years [36]. Furthermore, long-standing eosinophilic inflammation may increase the risk of esophageal remodeling with subsequent stricture formation. A recent study nicely showed how the prevalence of esophageal strictures correlates with the duration of untreated disease [37]. Eosinophils, eotaxin-3, and Th2 cytokines (IL-5 and IL-13) have been shown to be necessary for this esophageal tissue remodeling in EoE. In addition, swallowed topical corticosteroids and dietary interventions not only reduce this inflammation but may also prevent and even reverse this esophageal remodeling process in the long run [38]. Given the fact that PPI-REE and EoE share genotypic, phenotypical, and mechanistic features, there is concern that PPI-REE and EoE might share a similar risk of fibrostenotic complications if untreated, and hopefully, PPI therapy might impact on this natural history in PPI-REE. Two small retrospectives series of patients have shown that children with PPI-REE may

Table 3. Unsolved issues regarding diagnosis and treatment for PPI-REE

Etiology and pathogenesis of PPI-REE
Molecular biomarkers/genetic testing distinguishing PPI-REE from EoE
Natural history of PPI-REE
Doses, dosing interval, and duration required for initial PPI trial
Influence of PPI metabolism genotype (CYP2C19) in short- and long-term PPI response
Optimal PPI dosing as maintenance therapy
Rate of sustained remission on maintenance PPI therapy
Impact of allergen exposure on sustained PPI responsiveness
Need and frequency of endoscopy in follow-up

EoE eosinophilic esophagitis, *PPI* proton pump inhibitor, *PPI-REE* proton pump inhibitor-responsive esophageal eosinophilia

eventually progress to EoE [39, 40]. A recent abstract has first evaluated long-term response to PPI therapy in PPI-REE [41]. In 40 PPI-REE patients, acid suppressive therapy was progressively tapered based on clinical symptoms and maintained at the lowest dose with the target endpoint of clinical remission, with a follow-up endoscopy performed at 12 months or longer. Sustained clinico-histological remission on low-dose maintenance PPI therapy was observed in 64 % of adult PPI-REE patients. A majority of relapsers showed recurrent eosinophilic inflammation limited to the distal esophagus, which resolved after PPI dose intensification. Therefore, it might be uncommon for adult PPI-REE patients to fully lose PPI response and be reclassified as EoE.

Current guidelines [5•, 11, 12] suggest high-dose PPI therapy (20–40 mg once or twice daily in adults and 1 mg/kg per dose twice daily in children for 8–12 weeks). However, we lack comparative studies in terms of PPI molecule, doses, dosing interval and duration. PPIs undergo hepatic metabolism by the cytochrome P450 (CYP) system and the principal enzyme involved in the activation process of PPIs is *CYP2C19*. This genotype influences response to PPI therapy in PPI-based therapies, such as GERD or eradication therapy for *Helicobacter pylori* infection [42, 43]. A rapid metabolizer genotype, which is the most common genotype in Caucasian populations (56–81 %), may result in low plasma levels and lack of therapeutic effect of PPI therapy in PP-REE patients, both in the short and long term. Further studies should validate this hypothesis.

Compliance with Ethics Guidelines

Conflict of Interest

Javier Molina-Infante declares that he has no conflict of interest.
Alfredo J. Lucendo declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the authors.

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This is the first experimental study showing that GERD and EoE cells share the potential to express eotaxin-3 whenever stimulated by Th2 cytokines. Moreover, omeprazole was shown to block eotaxin-3 expression in both GERD and EoE patients. As such, PPI might have anti-inflammatory effects independent of acid suppression and a PPI response may not distinguish accurately between GERD and EoE.
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