



Proton-pump inhibitor-responsive esophageal eosinophilia

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Purpose of review

Proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) refers to patients showing symptoms and histological findings suggestive of eosinophilic esophagitis (EoE) who achieve complete remission on PPI therapy. This article aims to review evolving evidence on this novel phenotype over the last year.

Recent findings

Several prospective series have reported consistent rates of PPI-REE (30–40%) in adults with suspected EoE. At baseline, PPI-REE and EoE have been shown to be indistinguishable upon clinical, endoscopic, and molecular characteristics [eotaxin-3, interleukin (IL-5), and IL-13 expression]. PPI therapy partially restores esophageal mucosal integrity in PPI-REE, but not in EoE. Anti-inflammatory effects of PPI therapy, independent of acid suppression, have been confirmed in EoE and gastroesophageal reflux disease cell cultures. PPI therapy *in vivo* downregulates Th2 cytokines in PPI-REE patients, in a similar fashion to that seen in steroid-responsive EoE.

Summary

PPI-REE has emerged as a common clinical phenotype. PPI-REE and EoE remain largely indistinguishable, suggesting that they might be the same disease at baseline. While PPI therapy has been demonstrated to partially restore epithelial integrity in PPI-REE, *in-vitro* and *in-vivo* studies suggest that the anti-inflammatory effects of PPI therapy may be responsible for this restoration through inhibition of the Th2-allergic pathway rather than only acid suppression.

Keywords

eosinophilic esophagitis, gastroesophageal reflux disease, proton-pump inhibitor-responsive esophageal eosinophilia

INTRODUCTION

In the 2007 first consensus guidelines on eosinophilic esophagitis (EoE) management [1], EoE could be diagnosed in patients with dysphagia/food impaction, esophageal eosinophilic infiltration (>15 eos/HPF), and either absence of response to proton-pump inhibitor (PPI) therapy or normal esophageal acid exposure on pH monitoring. Therefore, it was suggested that either a response to PPIs or increased acid exposure on pH monitoring were consistent with gastroesophageal reflux disease (GERD). The premise underlying this recommendation was that GERD, as an acid peptic disorder, responded to the acid suppressing ability of PPI treatment. An illustrative example of this thinking is given in the first case report of proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE), published in 2006, in which two children and an adult with clinical, endoscopic, and histological data suggestive of EoE sustain complete histologic response to PPI therapy [2]. Interestingly, 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 the treatment with a PPI, implicating acid reflux as the underlying cause.’ By that time, however, some visionary authors posed the possibility that a distinction between GERD and EoE based upon PPI responsiveness might be too simplistic, given the potential mechanisms of interaction between these disorders [3]. In fact, these authors recommended a systematic trial of PPI

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KEY POINTS

- PPI-REE is a common clinical phenotype, affecting at least one-third of adult patients with esophageal symptoms and eosinophilia suggestive of EoE.
- PPI-REE and EoE remain largely indistinguishable without a trial of PPI therapy, suggesting that they might be one and the same disease.
- PPI therapy partially restores impaired esophageal mucosal integrity in PPI-REE, but not in EoE, underscoring the potential role of GERD in PPI-REE patients.
- Alternatively, experimental and clinical studies have shown anti-inflammatory effects of PPI therapy, through actions on eotaxin-3 and Th2 cytokines, that are independent of PPI effects on acid secretion.

therapy in all patients with an EoE phenotype (as we do today), proposing that a response to PPI therapy does not preclude a diagnosis of EoE. Indeed, these authors likely anticipated the potential anti-inflammatory effects of PPIs, independent of their effects on gastric acid production. In 2011, the first prospective series reporting that up to 50% of patients with an EoE phenotype at baseline might accomplish clinicohistological remission on PPI therapy was published [4]. Furthermore, neither a negative nor positive pH monitoring result predicted the favorable response to PPIs.

The description of this new phenotype, PPI-REE, was acknowledged as one of the major advances in EoE research in the updated 2011 consensus recommendations for EoE [5]. Within the past year, PPI-REE has been further emphasized in an updated clinical guideline [6] and the first systematic review on PPI-REE has been published as well [7], highlighting the growing importance of this topic, particularly in adult patients. The aim of this review

is to discuss further evolving evidence on the existence and meaning of PPI-REE.

PROSPECTIVE SERIES (ADULTS)

During the past year, a number of prospective series on PPI-REE in adults have been reported. Two large series from the United States have been published, comprising 60 and 66 patients [8,9], whereas two series from Czech Republic (*n*=26) and Spain (*n*=44) have been reported in abstract form [10,11]. The main results of these four studies, coupled with the prior prospective Spanish series, are summarized in Table 1 [12]. Of note, the prevalence of PPI-REE in patients evaluated for esophageal eosinophilia and characteristics of EoE varies between 35% and 50% among adult patients in these five studies, stressing the importance of PPI-REE in clinical practice.

RETROSPECTIVE SERIES (CHILDREN AND ADULTS)

One of the key questions in patients with PPI-REE is whether they remain a distinct phenotype or evolve into EoE. A retrospective series of seven pediatric patients with documented PPI-REE [13] reported two patients (28%) with recurrence of symptoms during maintenance PPI therapy (one of them with similar PPI dose, the other with half-dose than in the initial trial), who subsequently underwent endoscopy, showing relapsing esophageal eosinophilia. Therefore, these patients were reclassified as having EoE and PPI response was considered a transient phenomenon. This study is in line with other recent retrospective pediatric series, reporting a similar transient PPI response in four pediatric patients, despite similar or even higher PPI doses used as maintenance therapy [14]. As such, long-term follow-up in PPI-REE patients may be critical to promptly detect esophageal eosinophilia relapse and prospective studies addressing the long-term

Table 1. Prospective series in adult patients, from Europe and the United States, have shown consistent high rates of PPI-REE in patients with an EoE phenotype [12]

	N	Histological remission on PPI therapy	PPI dose
Molina-Infante <i>et al.</i> [4], Spain	35	50%	Rabeprazole 20 mg b.i.d.
Vazquez-Elizondo <i>et al.</i> [9], USA	36	36%	Omeprazole 20 mg b.i.d.
Martinek <i>et al.</i> [10], Czech Republic	26	Proximal 30.5 (0.2–80) to 4 (0–9) ^a	Omeprazole 20 mg b.i.d.
		Distal 36 (15–60) to 12 (0.9–25)	
Dellon <i>et al.</i> [8], USA	68	35%	PPI 20–40 mg b.i.d.
Molina-Infante <i>et al.</i> [11], Spain	44	40%	Omeprazole 40 mg b.i.d.

EoE, eosinophilic esophagitis; PPI-REE, proton-pump inhibitor-responsive esophageal eosinophilia.
^aEosinophils per high power field, mean (range).

efficacy of PPI therapy in PPI-REE patients are clearly warranted.

In adults, PPI therapy was clinically effective in a retrospective series from Japan in two out of six (33%) patients with an EoE phenotype [15]. However, histological response was not evaluated. This study corroborates previous data published recently in Japan, showing rates of PPI-REE (clinicohistologic and clinical response) of 42% and 60% in two small retrospective ($n = 12$) and prospective ($n = 5$) series, respectively [16,17].

THE CHALLENGE OF DISTINGUISHING PROTON-PUMP INHIBITOR-RESPONSIVE ESOPHAGEAL EOSINOPHILIA AND EOSINOPHILIC ESOPHAGITIS: ARE THEY THE SAME DISEASE?

As a PPI trial has been established as a necessary intervention before a diagnosis of EoE is confirmed [5,6^{***}], it will be important to learn how to differentiate EoE from PPI-REE so that those patients with initial PPI response who will evolve into EoE patients may be prospectively identified and followed carefully. In 2013, two studies conducted in adults, including 66 and 103 patients with >15 eos/HPF, respectively, failed to find distinguishing clinical, endoscopic, and histological features between patients ultimately found to have EoE or PPI-REE [8,18]. Moreover, the levels of eotaxin-3, interleukin (IL)-5, and IL-13 expression in the distal and proximal esophagus in 40 adult patients with >15 eos/HPF (60% EoE and 40% PPI-REE) were indistinguishable between the two patient groups [11^{***}]. The findings of a common cytokine pattern are consistent with calling PPI-REE a subphenotype of EoE, only distinguishable after specific therapy (i.e. PPIs). Undoubtedly, studies are needed to determine why only a subset of patients among a group with a similar phenotypic expression respond to PPI therapy. A recent promising genetic tool, the EoE diagnostic panel, showed a sensitivity and specificity of >95% in identifying pediatric and adult EoE, and in distinguishing between EoE patients in remission and controls [19]. Validation of this genetic tool for distinguishing EoE from PPI-REE is clearly warranted.

ADVANCES IN UNDERSTANDING PROTON-PUMP INHIBITOR-RESPONSIVE ESOPHAGEAL EOSINOPHILIA PATHOPHYSIOLOGY

Noteworthy advances aiming at clarifying PPI-REE pathophysiology have been accomplished over the last year, specifically on epithelial barrier

impairment and potential anti-inflammatory effects of PPI therapy.

Effect of proton-pump inhibitor therapy on esophageal eosinophilia-related epithelial barrier impairment

The prevailing hypothesis to explain PPI-REE has been that coexisting GERD might be the primary event, allowing the potential entry of food-derived allergenic molecules through acid-induced epithelial barrier damage in the esophagus [3]. In a series of experiments using rabbit esophageal epithelium, the normal esophagus was found to be virtually impermeable to epidermal growth factor, a peptide with a molecular weight of 6 kD, and to dextrans with a molecular weight of 4 kD [20]. In contrast, esophageal mucosa exposed to acid and pepsin became permeable to epidermal growth factor and to dextrans as large as 20 kD. 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. Recently, GERD-related impaired mucosal integrity through the dilation of esophageal epithelial intercellular spaces has been demonstrated to occur with either pathological or physiological esophageal acid exposure, at both distal and proximal esophagus [21]. Furthermore, acid and weak acidic perfusion of the distal esophagus has been shown to impair mucosal integrity in both the exposed distal esophagus and proximal, non-exposed esophagus [22], suggesting a whole organ response to a localized injury. Therefore, PPI therapy in PPI-REE would correct acid-related esophageal epithelial damage, preventing further allergen presentation as the first step in the pathway of EoE. An important study addressing this theory has been published [23^{***}]. Eleven patients with an EoE phenotype, but without a PPI trial, were compared to 11 controls at baseline. Esophageal mucosal integrity was measured in the distal esophagus, *in vivo* with a through-the-scope electrical tissue impedance spectroscopy 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 labeled 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. Patients with an EoE phenotype were then given omeprazole 40 mg b.i.d. and reevaluated 8 weeks later. After acid-suppressive therapy, mucosal integrity was partially restored in PPI-REE,

but not in EoE patients. The authors concluded that mucosal integrity impairment in PPI-REE might be because of GERD, whereas it might be related to inflammatory cell recruitment in EoE. Although pH measurements were not performed in this study, this important finding will help to elucidate mechanisms of injury in EoE and PPI-REE.

CAN GASTROESOPHAGEAL REFLUX DISEASE PRODUCE AN EOSINOPHILIC ESOPHAGITIS PHENOTYPE IN ATOPIC PATIENTS?

In 2009, a provocative experimental study demonstrated that GERD, in contrast to classic thinking, caused oesophageal inflammation through a cytokine-mediated mechanism rather than direct epithelial caustic injury [24]. 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 later progressed to the mucosal surface. Interestingly, mucosal erosions did not appear until post-operative 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 induce cytokine injury through a pathway similar to the Th2 pathway found in EoE but responsive to PPIs. In other words, the initiating event in the pathophysiology of PPI-REE might be GERD inducing an atypical inflammatory Th2 response, mimicking EoE, but responsive to PPI treatment. 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 [25¹¹], 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.

ANTI-INFLAMMATORY EFFECTS OF PROTON-PUMP INHIBITOR THERAPY

Eotaxin-3 is a potent eosinophil chemoattractant that plays a key role in trafficking eosinophils to the esophagus in EoE. The expression of eotaxin-3 is stimulated by Th2 cytokines, such as IL-4 and IL-13 (normally overproduced in allergic diseases), whose effects are mediated by the signal transducer and activator of the transcription (STAT)6 signaling pathway.

Improvement of esophageal symptoms with PPI therapy has been considered *prima facie* evidence of GERD. However, PPIs have been found to have antioxidant properties and direct effects on

eosinophils, neutrophils, monocytes, endothelial, and epithelial cells that might prevent inflammation, independent of their acid suppressing properties [26]. Furthermore, emerging translational research in experimental asthma and EoE demonstrates that PPIs might exert eosinophil-reducing effects. For example, in 2009, novel anti-inflammatory effects of PPIs were reported in murine asthma [27]. PPIs (including omeprazole, lansoprazole, and esomeprazole) inhibited in-vitro IL-4 and IL-13 signaling through STAT6, significantly reducing inflammatory cells (including eosinophils) in bronchoalveolar lavage fluid and lung sections. In 2013, an experimental study showed that omeprazole blocks Th2 cytokine-stimulated eotaxin-3 expression in oesophageal squamous cell cultures from both GERD and EoE patients [25¹¹]. As these experiments are conducted using in-vitro cultured esophageal epithelial cells, the observed PPI effects must be independent of their effects on gastric acid production. This study suggests that PPIs can have anti-inflammatory actions independent of their effects on acid-secretion and cast doubt on the assumption that a positive response to PPI therapy necessarily establishes a diagnosis of GERD. The same collaborative group has also reported that inhibition of IL-4 and IL-13 stimulated eotaxin-3 expression in EoE oesophageal cells is mediated through blocking STAT6 [28¹¹]. In light of these findings, a recent study has demonstrated for the first time *in vivo* that PPI therapy leads to a significant downregulation in gene expression of Th2-inflammatory markers in the distal and proximal esophagus, in 23 PPI-REE patients, similar to findings observed in EoE patients after topical steroids [11¹¹]. Finally, other recent experimental evidence has shown that IL-4 and IL-13 can promote eotaxin-3 secretion from both esophageal epithelial cells and fibroblasts. Unlike esophageal epithelial cells, Th2 cytokine-stimulated eotaxin-3 secretion by fibroblasts is not blocked by omeprazole, suggesting that PPIs might impact on mucosal inflammation but not on subepithelial fibrosis [29]. This suggests that those aspects of EoE pathophysiology that are modulated by PPIs cannot account for the complete pathologic manifestation of the disease.

CONCLUSION

PPI-REE is a common clinical phenotype (at least 33%) in adult patients with esophageal eosinophilia and symptoms. PPI-REE and EoE remain largely indistinguishable without a trial of PPI therapy, suggesting that they might be manifestations of a similar disease. PPIs have been shown to partially restore distal esophageal mucosal integrity in PPI-REE patients, but not in EoE. Several studies have

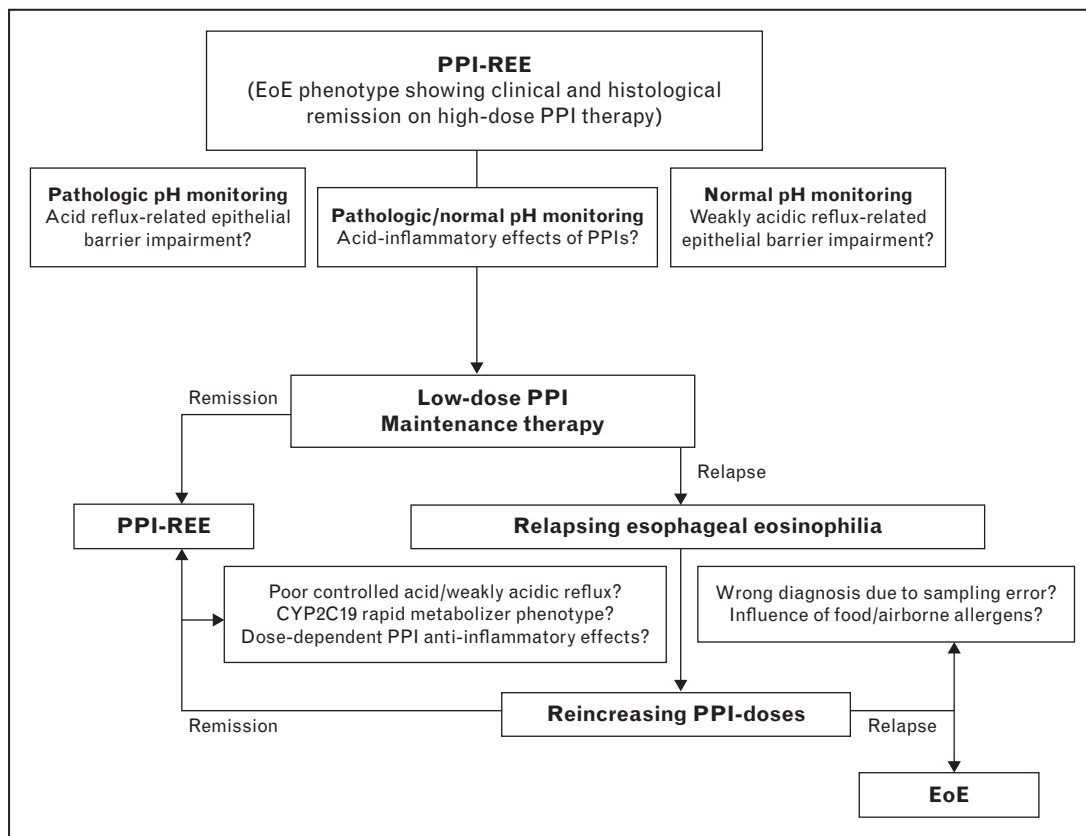


FIGURE 1. Interplaying factors and potential explanations for long-term outcomes in PPI-REE. PPI-REE, proton-pump inhibitor-responsive esophageal eosinophilia.

demonstrated in-vitro and in-vivo anti-inflammatory effects of PPIs, independent of their effects on gastric acid secretion, through inflammatory modulation of the Th2 pathway. We summarize evolving concepts and unmet needs in PPI-REE in the list below.

- (1) PPI-REE occurs commonly in adult patients with an EoE phenotype.
- (2) At baseline (before a PPI trial), PPI-REE is indistinguishable from EoE (clinical, endoscopic, pathologic, and molecular findings), suggesting that they might be the same disease.
- (3) It remains unknown why only a subset of patients with an EoE phenotype respond to PPI therapy. Studies addressing genetic differences in patients with a similar phenotypic expression are warranted.
- (4) PPI-REE is more common in patients with concomitant GERD, but GERD (or at least, pathological acid exposure) is not necessary for PPI-REE to occur.
- (5) Distal esophageal mucosal integrity is impaired in both EoE and PPI-REE. PPI therapy partially restores the mucosal barrier in PPI-REE, but not in EoE, supporting the possibility that barrier healing in PPI-REE may prevent allergen presentation in the esophagus.
- (6) Esophageal barrier impairment may occur with exposure to acidic and weakly acidic reflux, therefore calling into question the validity of a rigid classification of PPI-REE patients (GERD and non-GERD patients) based upon pH monitoring results.
- (7) Recent studies have shown that eotaxin-3 expression in GERD and EoE cell cultures is similar when stimulated with Th2 cytokines, suggesting that emerging allergies may be changing the classical face of GERD.
- (8) Several recent studies have demonstrated in-vitro and in-vivo anti-inflammatory effects of PPI through modulation of the Th2 pathway, independent of acid suppression.
- (9) The long-term efficacy of PPI therapy in PPI-REE patients is unknown.
- (10) The importance of CYP2C19 genotype for PPI response in PPI-REE patients, similarly to GERD or *Helicobacter pylori* treatment, has not been evaluated yet.

Figure 1 summarizes the long-term, potential outcomes of PPI-REE.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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