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Proton Pump Inhibitors for Eosinophilic Esophagitis

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Abstract

Purpose of review—To review the significance and plausible mechanisms underlying “proton pump inhibitor (PPI)-responsive esophageal eosinophilia” in eosinophilic esophagitis (EoE).

Recent findings—EoE is defined as an immune-mediated clinicopathologic condition characterized by esophageal dysfunction and eosinophil-predominant inflammation. This new conceptual definition has been proposed partly due to a recently identified disease phenotype called “PPI-responsive esophageal eosinophilia”. Emerging data support the possibility that this condition represents a clinical response to anti-inflammatory properties of PPIs that are independent of effects on gastric acid.

Summary—Currently, the diagnosis of EoE is reserved for patients with esophageal eosinophilia and symptoms that do not respond to PPIs. This practice may not be appropriate, however, both because gastric acid suppression by PPIs might benefit EoE patients and because PPIs have anti-inflammatory properties that also might benefit EoE patients. More studies are sorely needed to understand the mechanisms underlying PPI-responsive esophageal eosinophilia. Presently, a favorable response to PPI therapy should not be regarded as proof of an underlying acid-peptic disorder like GERD, nor should it preclude a diagnosis of EoE. Furthermore, it seems prudent to recommend a trial of PPI therapy for patients with esophageal eosinophilia and symptoms, even when the diagnosis of EoE seems clear-cut.

Keywords

Eosinophilic esophagitis; GERD; proton pump inhibitors

Introduction

The role of proton pump inhibitor (PPI) therapy in eosinophilic esophagitis (EoE) has become increasingly perplexing over the last decade despite numerous advances in our understanding of the pathogenetic mechanisms underlying this disorder. Initially, a trial of PPI therapy was recommended to distinguish EoE from gastroesophageal reflux disease (GERD), a disorder known to share a complex relationship, similar symptoms and histological findings with EoE [1]. The premise underlying this recommendation was that inhibition of gastric acid secretion was the only important effect of proton pump inhibitors,

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Conflicts of Interest

There are no conflicts of interest.

and therefore only an acid-peptic disorder like GERD could respond to PPI treatment. However, recent studies and clinical observations on patients with a clinical condition termed “PPI-responsive esophageal eosinophilia” have called this assumption into question. Furthermore, a number of potential anti-inflammatory effects of proton pump inhibitors have been described [2], suggesting that proton pump inhibitors might have anti-inflammatory actions independent of their effects on gastric acid secretion. The purpose of this paper is to review the phenomenon of “PPI-responsive esophageal eosinophilia” and potential mechanisms of action for PPIs in EoE.

PPI-Responsive Esophageal Eosinophilia

Esophageal eosinophilia was once regarded primarily as a histologic feature of GERD. In 1982, Winter *et al.* reported that the finding of eosinophils in the esophageal epithelium could be used as a diagnostic criterion for reflux esophagitis in children [3]. The presence of intraepithelial eosinophils in the esophagus was found to correlate with abnormal acid clearance determined by esophageal pH probe monitoring. In particular, intraepithelial eosinophils were found in all levels of the esophagus, and involvement of the proximal esophagus was associated with the greatest abnormalities in esophageal acid exposure. A number of subsequent reports supported the contention that esophageal eosinophilic infiltration was associated with gastroesophageal reflux disease [4–6]. However, later in the 1990s, several case series described dense esophageal eosinophilia in adults and children presenting with dysphagia, food impaction, or severe reflux symptoms [7–11]. Not only did the patients have endoscopic findings of esophageal rings and linear furrows that were atypical for reflux esophagitis, but they also had other features uncharacteristic of GERD such as normal esophageal pH monitoring studies, no response to PPI therapy, and improvement after elimination of food allergens. These features suggested an allergic etiology. Furthermore, a study by Steiner *et al.* reported an inverse correlation between reflux index and eosinophil infiltration in children who underwent same day esophageal endoscopy with biopsies and 24-hour esophageal pH monitoring [12]. These reports introduced the idea of eosinophilic esophagitis as an emerging disease entity distinct from GERD. In response to clinical confusion regarding this new disease, the first international gastrointestinal eosinophilic research symposium (FIGERS) developed a consensus statement defining eosinophilic esophagitis as a clinicopathologic disorder of the esophagus with upper GI tract symptoms, ≥ 15 eosinophils/hpf on mucosal biopsy, and the absence of pathologic GERD as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to high-dose PPI medication [1].

As eosinophilic esophagitis became more widely recognized, it became increasingly evident that the distinction between EoE and GERD was not always a clear one. Clinical series reported that 26 – 56% of patients with EoE (diagnosed by the histological criteria of ≥ 15 eosinophils/hpf on biopsy) had abnormal esophageal acid exposure detected by esophageal pH monitoring [13–16]. A number of potential mechanisms have been proposed to explain the complex, synergistic interaction between the two disorders [17]. Although the original FIGERS criteria held that a response to high-dose PPI therapy or a normal esophageal pH monitoring study precluded a diagnosis of EoE, recent studies have identified a subgroup of patients with typical EoE symptoms and endoscopic abnormalities, and who demonstrate a

clinicopathologic response to PPI therapy despite having no evidence of GERD by endoscopy or pH/impedance-monitoring studies [15,16,18–26]. This group of patients has been described as having “PPI-responsive esophageal eosinophilia” in the 2011 updated consensus statement, which now defines eosinophilic esophagitis conceptually as a chronic, immune-driven disorder [27**].

Two prospective studies have demonstrated that PPI-responsive esophageal eosinophilia represents a *bona fide* disease phenotype. In a study by Peterson *et al.*, 30 patients diagnosed clinically and histologically with EoE were randomly assigned to treatment with either esomeprazole or fluticasone [15]. After 8 weeks of treatment, there was no significant difference between the groups in the rates of clinical and histological remission. Twenty-five percent of patients in the esomeprazole group responded to therapy, and baseline esophageal pH monitoring results were not useful for predicting response to either drug. A study by Molina-Infante *et al.* systematically examined 35 patients with esophageal eosinophilia, and 75% responded to an 8-week trial of treatment with rabeprazole [16**]. More specifically, 2 out of 6 subjects with normal pH probe studies and no endoscopic evidence of reflux achieved clinicopathologic remission with PPI treatment [16]. These studies along with the new consensus guidelines provided the basis for subsequent studies to determine the significance of this eosinophilic disease phenotype.

More recent studies have paid particular attention to this group of patients in order to identify any distinctive clinical and histological attributes. Dohil *et al.* retrospectively analyzed four pediatric patients with PPI-responsive esophageal eosinophilia and found that inflammatory cells including eosinophils, mast cells, and CD45RO memory T cells reaccumulated in the esophagus over a 3–12 month period, suggesting that PPI-responsive esophageal eosinophilia may be only a transient phenomenon [18*]. A complimentary study by Levine *et al.* retrospectively reviewed 38 pediatric patients diagnosed with EoE and treated with long-term PPI monotherapy (3.0 ± 2.4 years) to evaluate the efficacy of PPIs as a maintenance therapy [25*]. Although the majority of patients (28 of 36) had histological inflammation (≥ 15 eosinophils / hpf on recent biopsies) found at long-term follow-up, all of the patients had improved symptomatically. Interestingly, the degree of subepithelial fibrosis did not worsen despite persistent esophageal inflammation. This study emphasizes that PPIs can result in symptomatic improvement in eosinophilic esophagitis, even if they do not result in histological remission defined by < 5 eosinophils/hpf. Lastly, a study by Schroeder *et al.* examined eosinophil peroxidase staining, histological and clinical features of patients thought to have EoE, and could not identify any feature that distinguished patients with persistent PPI-responsive esophageal eosinophilia (n=5) from those who were transient PPI-responders (n=2) or PPI-non-responders (n=27) [28*]. As more investigational studies develop, subcategorizing esophageal eosinophilia to GERD (detected by esophageal pH monitoring and/or endoscopy), PPI-responsive esophageal eosinophilia, transient PPI-responder, PPI-non-responder EoE (or “classic” EoE), and coexisting EoE-GERD may be necessary to study the mechanism underlying PPI-responsive esophageal eosinophilia. It is conceivable that these patients with PPI-responsive esophageal eosinophilia simply have GERD that is not detectable by endoscopy and esophageal pH monitoring, but that responds to the antisecretory effects of PPIs nevertheless. Alternatively, these patients may indeed

have EoE that responds to therapeutic effects of PPIs that are independent of their effects on gastric acid secretion.

Potential Mechanism of Proton Pump Inhibitors in EoE

The most well studied effect of proton pump inhibitors 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 where proton pump inhibitors are acid-activated. The active form of the drug then forms covalent disulphide bonds with cysteine residues on the ATPase, rendering the pumps inactive [29]. Acid suppression might be beneficial in EoE because, as mentioned above, acid esophageal reflux might contribute to esophageal inflammation in this condition [17]. 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 [30]. Acid exposure can enhance the expression of adhesion molecules (e.g., vascular cell adhesion protein-1) and cytokines (e.g., interleukin-8 and interleukin-1 β), and cause the release of other inflammatory mediators (e.g., mast cell products) in the esophagus, possibly leading to the recruitment of eosinophils and other immune cells [31–33]. Furthermore, patients with EoE may have esophageal hypersensitivity to acid-induced pain [23], and thus suppressing gastric acid secretion with PPIs might provide symptomatic relief even for patients with normal esophageal acid exposure. Additional studies elaborating the role of esophageal acid exposure in EoE pathogenesis are needed to clarify the all the potential benefits of acid suppression.

Interestingly, new and emerging data suggest that PPIs may benefit patients with EoE through effects that are independent of gastric acid suppression. Two recent studies have shown that PPIs inhibit Th2 cytokine-stimulated secretion of eotaxin-3, the primary eosinophil chemoattractant in EoE, in esophageal squamous epithelial cells [34**,35**]. Both omeprazole and lansoprazole exhibited this inhibition, suggesting a class effect of PPIs. This inhibition occurred with omeprazole concentrations as low as 1 μ M, which are physiologically achievable in blood with conventional oral dosing or intravenous administration [36,37]. Mechanistically, the inhibitory effect of PPIs seem 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.

These experiments utilized acid-activated PPIs [34,35], and it is not clear whether acid activation of these medications can occur in the esophagus. PPIs are known to accumulate and become activated in an acidic tissue microenvironment, which is found frequently in gastric parietal cells. However, immune cells, including eosinophils and neutrophils, also can release protons from their exocytic granules and lysosomes into the microenvironment [38–40]. Microenvironment acidification has been documented in the setting of inflammation associated with infection, asthma, and rheumatoid arthritis [41–43]. Gastroesophageal acid reflux also might acidify the esophageal microenvironment, and the Na^+/H^+ exchanger on esophageal epithelial cell membranes is known to extrude intracellular

protons that accumulate in the setting of injury in order to maintain intracellular pH [44]. Thus, there are a number of plausible mechanisms whereby PPIs might be activated in an acidic microenvironment of the esophagus that is inflamed by eosinophilic esophagitis with or without acid reflux.

Overall, these experiments elucidate molecular mechanisms whereby patients with Th2 cytokine-driven esophageal eosinophilia can respond to PPIs, independent of effects on gastric acid secretion. These findings might explain the phenomenon of PPI-responsive esophageal eosinophilia, and suggest that even patients who have EoE without acid reflux present might benefit from PPI therapy. Nevertheless, further studies are needed to establish that these PPI effects observed *in vitro* are applicable to patients.

Other Anti-inflammatory Effects of Proton Pump Inhibitors

In addition to the mechanisms described above, proton pump inhibitors have been found to have a number of other potentially beneficial biological actions that are independent of their anti-secretory effects [2]. For example, proton pump inhibitors have demonstrable anti-oxidant properties including scavenging for hydroxyl radicals and inhibiting oxidation mediated by transition metals like copper and iron [45–48]. PPIs have also been found to inhibit certain immune cell functions, particularly neutrophil functions such as oxidative burst, migration, and phagocytosis [49,50]. PPIs can exert anti-inflammatory effects by decreasing adhesion molecule and pro-inflammatory cytokine (e.g., interleukin-8, interleukin-6, tumor necrosis factor- α) production by endothelial and epithelial cells [2,51,52]. In epithelial and non-epithelial cells, Cortes *et al.* found that omeprazole decreased Th2 cytokine-induced STAT6 phosphorylation, an effect that they attributed to the alkylating ability of the proton pump inhibitor [53]. All these reported anti-inflammatory effects may influence a variety of inflammatory disorders including EoE, and further studies are needed to examine these effects.

Conclusions

Currently, the clinical recommendations put forth by TIGERS in the 2011 consensus update 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) to identify GERD-associated esophageal eosinophilia and PPI-responsive esophageal eosinophilia. Through the potential mechanisms discussed above, furthermore, EoE patients almost might benefit from PPI therapy whether or not they have co-existing GERD. More studies are sorely needed to recognize, define, and mechanistically understand PPI-responsive esophageal eosinophilia. For now, it seems prudent to recommend a clinical trial of PPI therapy for patients with esophageal eosinophilia and symptoms, even when the diagnosis of EoE seems clear-cut. Given the data reviewed above showing that PPIs have anti-inflammatory effects independent of gastric acid suppression, however, a favorable response to PPI therapy should not be interpreted as proof for an underlying acid-peptic disorder nor should such a response preclude a diagnosis of EoE.

Acknowledgments

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* of special interest

** of outstanding interest

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Key points

- The term “PPI-responsive esophageal eosinophilia” describes a subgroup of patients who have typical EoE symptom presentation, have had GERD excluded by endoscopy and/or pH/impedance-monitoring studies, and yet demonstrate a clinicopathologic response to PPI therapy.
- More investigational studies are needed to recognize, define, and mechanistically understand PPI-responsive esophageal eosinophilia.
- PPIs have anti-inflammatory effects independent of their effects on gastric acid secretion and, therefore, a favorable response to PPI therapy should not be interpreted as proof for an underlying acid-peptic disorder nor preclude a diagnosis of EoE.