Proton Pump Inhibitor Therapy for Eosinophilic Esophagitis: A Paradigm Shift

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Eosinophilic esophagitis (EoE) is a chronic local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (≥15 eosinophils per high power field) (1). First described in the early 90s (2), it currently constitutes the most prevalent cause of chronic esophagitis after gastroesophageal reflux disease (GERD) and the leading cause of dysphagia and food impaction in children and young adults (1). Without question, the consideration of proton pump inhibitor (PPI) therapy within the diagnostic and/or therapeutic algorithm has been the most evolving topic over the past decade in the field of EoE. Major advances in this field have been accomplished or endorsed by European researchers, especially from Spain. This study aims to provide a historical view on these challenging changes, which are summarized in **Table 1**.

2007: RESPONSE TO PPI THERAPY IS A DIAGNOSTIC TOOL THAT RULES IN GERD AND RULES OUT EOE

In the 2007 first consensus guidelines on EoE management (3), the disease could be diagnosed in patients with compatible clinic and histologic data after demonstration of either absence of response to PPI therapy or, alternatively, a normal acid exposure time on esophageal pH monitoring. Therefore, it was suggested that either remission on PPIs or increased acid exposure on pH monitoring were consistent with GERD and ruled out EoE. The premise underlying this recommendation was that GERD, as an acid peptic disorder, was the only esophageal disorder that could respond to the acid suppressing ability of PPI treatment. This thinking was clearly illustrated in the first series of three patients with clinical, endoscopic and histologic data suggestive of EoE, who achieved complete remission on PPI therapy, published in 2006 (4). The authors 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."

It is important to stress that 2007 recommendations established a dichotomous distinction between patients, which could be diagnosed with either GERD or EoE upon response to PPI therapy/pH results, but could not have both disorders concomitantly. These diagnostic criteria were counterintuitive, since the likelihood of coexistence of GERD and EoE (more common in young male population) was *a priori* high. By that time, some visionary authors posed the possibility that this rigid distinction between GERD and EoE could be simplistic, given the potential mechanisms of interaction between both disorders (5).

2011–2013: RESPONSE TO PPI THERAPY IS A DIAGNOSTIC TOOL THAT RULES IN GERD/PPI-RESPONSIVE ESOPHAGEAL EOSINOPHILIA AND RULES OUT EOE

Contrary to consensus guidelines, two retrospective pediatric studies from 2009 showed that response to PPI therapy was common (40%) and not necessarily dependent on results of normal/abnormal pH studies in patients with symptomatic esophageal eosinophilia suggestive of EoE (6,7). In 2011, a first prospective series from Spain systematically evaluating response to PPI therapy showed that up to 50% of patients with suspected EoE were responders to PPIs (8). Interestingly, there was a relevant overlap between GERD and EoE: among patients with pathological pH monitoring, 20% did not achieve histologic remission on high-dose PPI therapy. Conversely, complete remission on PPIs was accomplished in 33% with normal pH monitoring. This study led to significant changes in diagnostic criteria, leading to withdrawal of esophageal pH monitoring (9,10). However, disease remission on PPI therapy was still considered sufficient to rule out EoE in subsequent guidelines published in 2011 and 2013 (9,10).

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2017: PPI THERAPY AS A TREATMENT FOR EOE. RESPONSE TO PPIS NEITHER CONFIRMS GERD NOR PRECLUDES EOE

EoE is well known to be a chronic immune-mediated disorder characterized by an aberrant Th2 inflammatory response involving interleukin (IL)-5 and IL-13 and local production of CCL26 (eotaxin-3), a chemokine that specifically attracts eosinophils to the esophageal mucosa. When activated, the eosinophils cause local tissue damage and recruit and/or activate other effector cells, such as mast cells, key modulators of esophageal fibrous remodelling (1). Moreover, the genetic basis of EoE has just recently defined through whole-genome transcript expression profiling of esophageal tissue (11). The EoE diagnostic panel, made up of 94 EoE genes, was shown to adequately distinguish patients with EoE from GERD and control subjects (11).

As for patients with PPI-responsive esophageal eosinophilia (PPI-REE), two studies published in 2014, from Spain and the Netherlands, demonstrated that baseline expression of markers of eosinophilic inflammation and genes modulating mast cell signature or involved in Th2 associated allergic inflammation (including CCL26, IL-5, IL-13, thymic stromal lymphopoietin, and periostin) in esophageal tissue largely overlaps in non-responders and responders to PPI therapy (12,13). In addition, two recent studies have shown that patients with PPI-REE showed a transcriptome that nearly completely overlapped with non-responders to PPIs, including the hallmark EoE genes for eosinophil chemotaxis (*CCL26*), barrier molecules (desmoglein *DSG1*), tissue remodeling (*POSTN*), and mast cells (*CPA3*) (14,15). This genetic profile that constitutes a diagnostic panel was radically different from that observed in patients with GERD and control subjects.

Furthermore, recent clinical studies from Spain, the Netherlands and United States have shown that PPI monotherapy in PPI-REE patients can almost completely reverse the Th2 signature and normalize the EoE diagnostic panel expression (12–14). These effects are similar to those exerted by anti-inflammatory drugs, like topical steroids or anti IL-13 biological drugs, used for EoE patients. Finally, two recent series from the United States and Spain have lately revealed that EoE patients initially responders to diet and topical steroid therapy were eventually found to be also responders to PPI therapy, and *vice versa* (16,17). These findings suggest that acid might be a contributor to antigen-mediated esophageal eosinophilia, besides posing the possibility that the three major therapeutic pillars for EoE (PPIs, elimination diet, and topical steroids) might be potentially interchangeable in a subset of patients.

Consequently, there is no rational basis to distinguish between patients with symptomatic esophageal eosinophilia based on a different response to a given drug. In fact, it seems counterintuitive to differentiate responders and non-responders to PPI therapy when their phenotypic, molecular, mechanistic, and therapeutic features cannot be reliably distinguished. A recent international multidisciplinary consensus position paper endorsed by the European Society of Eosinophilic Esophagitis has supported this concept of abandoning the artificial term "PPI-REE" (18). Contrary to the 2007 (3), 2011 (9) and 2013 (10) guidelines, response to PPIs cannot be considered a diagnostic exclusion criterion for EoE anymore, as PPI therapy is now deemed to be a potential therapeutic agent for all patients with clinic, endoscopic, and histologic features suitable for EoE (1). These changes in diagnostic criteria for EoE have been first proposed in the updated evidence-

Table 1. Evolving considerations over the past decade on response to PPI therapy in patients with clinic and histologic data compatible with EoE

2007 (3)	2011–2013 (9,10)	2017 (1)
Response to PPIs is a diagnostic tool that rules in GERD and rules out EoE	Response to PPIs is a diagnostic tool that rules in GERD or PPI-REE and rules out EoE	EoE and GERD are not mutually exclusive disorders and may coexist, albeit not necessarily interacting. Response to PPIs neither confirms GERD nor excludes EoE. PPIs are one the available therapies for patients with suspected EoE
A pathological pH monitoring is equivalent to either response to PPIs or GERD	Response to PPIs might occur with either normal or pathological pH monitoring	A pathological pH monitoring might be informative of GERD, but it does not neither prove a casual role for GERD nor predicts response to PPIs
Gastric acid inhibition is the only important effect of PPIs	Novel anti-inflammatory effects for PPIs are demonstrated in esophageal culture cells. These effects are independent of gastric acid inhibition	PPI monotherapy in PPI-REE downregulates Th2 inflammation and normalizes gene expression associated to EoE, in a similar way to that observed for topic steroids in EoE
GERD, as an acid-related disorder, is the only showing response to the acid-suppressing ability of PPIs	PPI-REE is a new intermediate phenotype, different from EoE, referring to patients with suspected EoE achieving complete remission on PPI therapy	PPI-REE is an inappropriate disease descriptor, arbitrarily based on a response to a single drug. Among EoE patients, responders and non-responders to PPIs show overlapping phenotypic, molecular, mechanistic, and therapeutic features
Acid reflux does not contribute to antigen-mediated esophageal eosinophilia	—	Acid reflux might contribute to antigen-mediated esophageal eosinophilia, as some responders to elimination diets were ultimately found to be also responders to PPIs

EoE, eosinophilic esophagitis; GERD, gastro-esophageal reflux disease; PPIs, proton pump inhibitor therapy; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia.

Table 2. Evolving changes in diagnostic criteria for EoE over the past decade

2007 (3)	Symptoms of esophageal dysfunction	Esophageal eosinophilic infiltration ≥15 eosinophilis per high power field	Lack of response to PPIs or a pathological pH monitoring	Other systemic and local causes of esophageal eosinophilia should be excluded, including GERD
2011–2013 (9,10)	Symptoms of esophageal dysfunction	Esophageal eosinophilic infiltration ≥15 eosinophilis per high power field	Lack of response to PPIs	Other systemic and local causes of esophageal eosinophilia should be excluded, including GERD and PPI-REE
2017 (1)	Symptoms of esophageal dysfunction	Esophageal eosinophilic infiltration ≥15 eosinophilis per high power field	—	Other systemic and local causes of esophageal eosinophilia should be excluded, but not GERD or PPI-REE

EoE, eosinophilic esophagitis; GERD, gastro-esophageal reflux disease; PPIs, proton pump inhibitor therapy; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia.

based guidelines (1), fully supported by the United European Gastroenterology, European Society of Eosinophilic Esophagitis, the European Academy of Allergy and Clinical Immunology and the European Society for Paediatric Gastroenterology Hepatology and Nutrition. Changes in diagnostic criteria for EoE over the past decade are displayed in **Table 2**.

SUMMARY

Up until recently, clinic and histologic remission on PPI therapy were systematically considered to rule in GERD and rule out EoE in patients with symptomatic esophageal eosinophilia. Therefore, GERD and EoE were mutually exclusive disorders. The recognition of patients with a clear EoE phenotype that achieved complete remission on PPIs, with or without GERD, was split from EoE under the artificial term PPI-REE. Growing evidence, mostly from Europe, over the past 5 years has demonstrated that phenotypic, molecular, and mechanistic features cannot be reliably distinguished between PPI-REE (responders to PPI therapy) and EoE (non-responders to PPI therapy). Therefore, European updated position papers and evidence-based guidelines have included responders to PPI therapy within the spectrum of EoE, abandoning the term PPI-REE. In addition, PPI monotherapy has been shown to effectively downregulate Th2 inflammation and normalize the gene expression associated to EoE, in a similar way to that observed for topic steroids. Consequently, PPI therapy is not a diagnostic tool anymore for EoE, but rather a therapeutic asset along with diets and topical corticosteroids for EoE.

Further research on the potential anti-inflammatory effects of PPIs (19), the interacting mechanisms between GERD and EoE, and the role of novel acid suppressing drugs in EoE, such as vonoprazan (20), are definitely warranted to elucidate the intricate relationship between GERD, EoE, and PPI therapy.

CONFLICT OF INTEREST

Guarantor of the article: Javier Molina-Infante, MD, PhD.
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