Published in final edited form as:

Gut. 2017 May ; 66(5): 979–980. doi:10.1136/gutjnl-2016-312601.

Proton pump inhibitor-responsive oesophageal eosinophilia: too early to change clinical practice

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We read the article by Molina-Infante *et al*¹ with great concern as it proposes a major change in the current practice guidelines for managing patients presenting for care by gastroenterologists worldwide. Proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE)¹ is characterised by an eosinophilic infiltrate of the oesophageal epithelium that is responsive to PPI therapy alone. The authors suggest that endoscopies should be performed prior to a therapeutic trial of PPI, so as not to miss this subtype of eosinophilic oesophagitis (EoE). We maintain that these two entities not only have yet to be proven to be the same pathophysiological process, but also that performing an initial endoscopy with biopsy would not change the current practice of first using a PPI before or after the diagnosis of oesophageal eosinophilia. The terms 'oesophageal eosinophilia' and 'eosinophilic oesophagitis' have not been proven to be interchangeable. Changing clinical practice, as the authors suggest, will lead to unnecessary endoscopies, diagnostic confusion and misdiagnosis of patients.

Although PPI-REE and EoE have an overlap in transcriptome analysis, significant difference exist. For example, there is a distinct change in expression of *KCNJ2*, a *potassium channel gene*, resulting in 72% sensitivity and 72% specificity to predict PPI-REE-pre versus EoE,

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Contributors ABM, M-LW, JMS and DM: manuscript writing. JM and GF: critical review of manuscript. CAL: manuscript writing and acquisition of data.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

accounting for the response due to PPI.² Even though they appear identical histologically and endoscopically, it is probable that they represent two distinct disease entities with the same histological endpoint—eosinophilic inflammation. Furthermore, *in vitro* studies, which suggest that PPIs inhibit cytokine-mediated eotaxin-3 expression, used concentrations up to 20 times the peak serum concentration of daily dosing.³ Clinical pharmacokinetic studies of 30 mg once daily lansoprazole have shown that peak serum concentrations (C_{max}) occur 1.5 hours following the daily dose of a PPI while serum concentrations remain well below 200 ng/mL for the majority of the day,⁴ well below those used in experimental *in vitro* models. The true exposure of PPIs in the oesophageal mucosa is unknown and the effects of physiological concentrations of PPIs on the oesophageal epithelium remain uncertain.

Clinically, there is concern that PPI-REE and EoE represent two different processes. In EoE, an antigen-/immune-mediated disease, dietary restriction and topical swallowed steroids have been shown to improve clinical symptoms and histopathology and can often be used interchangeably. In contrast, in our experience at The Children's Hospital of Philadelphia, over the last 5 years, we have seen 317 patients for second opinions related to the diagnosis of EoE. Of these, more than 50% were re-evaluated and were determined to be misdiagnosed (2011 EoE guidelines)—117 patients (37%) were initially diagnosed with EoE, were unresponsive clinically and histologically to dietary restriction and/or topical corticosteroid therapy and were never treated with a PPI. After being treated with a PPI, these patients had a complete or near complete response to PPI therapy. Thus, PPI therapy is not interchangeable with other therapies for EoE.

Finally, there is also concern about the effects that these new guidelines will have on the clinical application of PPIs and unnecessary endoscopies by gastroenterologists, especially in paediatrics. Paediatric patients who are placed on PPI therapy for reflux, dysphagia or presumed EoE almost universally undergo an upper endoscopy with biopsy if symptoms persist within 6–12 months after beginning on chronic PPI therapy. However, if symptoms resolve, PPI therapy can be discontinued and patients may never require an endoscopy. Because a PPI would almost always be the drug of choice for clinical symptoms, until definitive evidence proves that PPI-REE and EoE are interchangeable, an initial endoscopy may not always be warranted and may lead to the wrong diagnosis and suboptimal management of patients.

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