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Clarifying misunderstandings and misinterpretations about proton pump inhibitor-responsive oesophageal eosinophilia

Javier Molina-Infante[1], **Ikuo Hirano**[2], **Stuart J Spechler**[3] **PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS)**

[1]Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain

[2]Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[3]Department of Internal Medicine, VA North Texas Health Care System, and the University of Texas Southwestern Medical Center, Dallas, Texas, USA

We appreciate the interest of Muir *et al*[1] in our Position Paper on proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE).[2] Their letter highlights the ongoing controversies related to PPI-REE, particularly regarding practical diagnostic concerns in paediatric patients. We would like to address several issues raised by the authors:

1. When the clinical presentation is consistent with gastro-oesophageal reflux disease (GORD), an empiric trial of PPI therapy is always appropriate. Teenagers and adults with dysphagia, however, should undergo an endoscopic procedure, because dysphagia is a red-flag symptom. In adult patients with dysphagia and suspected eosinophilic oesophagitis (EoE), a baseline endoscopy off PPI therapy has diagnostic value. This approach has not led to unnecessary endoscopies or diagnostic confusion, as suggested by Muir *et al.*[1] Instead, it has elucidated the existence and improved our understanding of PPI-REE in adult patients.[2] The different and more non-specific clinical presentation of EoE in children (including feeding problems, heartburn, vomiting and abdominal pain) poses a diagnostic challenge for paediatricians, who should balance risks/benefits and uncertainties (see below) of empiric PPI therapy versus endoscopic procedures in these patients. Further studies are required to determine the best initial strategy in children, which is currently individualised depending on the clinical scenario.

2. The authors suggest that if symptoms suggestive of EoE resolve on an empiric trial of PPI therapy, ‘the drug can be discontinued and paediatric patients may never require an endoscopy’.[1] However, EoE is by definition a clinical and histological disease and neither of these parameters should be interpreted in isolation. Additionally, symptoms in children may be under appreciated due to difficulties describing their symptoms and behavioural adaptations, like food

Correspondence to Dr Javier Molina-Infante, Department of Gastroenterology, Hospital San Pedro de Alcantara, Pablo Naranjo s/n, Caceres 10003, Spain; xavi_molina@hotmail.com.

Contributors JM-I, IH and SJS contributed equally to this letter.

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avoidance and diet modification. Symptom response to PPI therapy is not specific either and may be observed in patients with GORD, PPI-REE, EoE, peptic ulcer and functional dyspepsia.[2] Furthermore, oesophageal symptoms have lately shown a modest capacity to predict the biological activity of EoE in adult patients.[3] Therefore, endoscopy with oesophageal biopsies remains instrumental to improve our diagnostic accuracy beyond a reliance on a symptom response to PPI therapy.

3. We never stated that 'oesophageal eosinophilia' and 'EoE' are interchangeable, but made the case that 'PPI-REE' and 'EoE' may not be distinct disorders. Like the vast majority of medical diseases, we do not believe that PPI-REE should be defined by a response to a medication, especially when clinical, endoscopic, histological, molecular, genetic and therapeutic parameters document substantial overlap between PPI-REE and EoE.[2]

4. A single change in the expression of one (KCNJ2, a potassium channel gene) out of 95 genes that are similarly up or down-regulated in oesophageal tissue of EoE and PPI-REE patients,[4] does not necessarily establish a different disease process.

5. The authors correctly noted that in vitro studies used relatively high omeprazole concentrations, that are not achieved in blood with conventional PPI dosing.[5] However, another publication has demonstrated PPI effects on inhibiting cytokine-stimulated secretion of eotaxin-3 using concentrations of omeprazole as low as 1 nm, which are achievable in blood with conventional dosing.[6]

6. We do agree with the fact that it remains unknown whether oesophageal inflammation in PPI-REE is primarily induced by acid reflux disease or antigen exposure. However, GORD and EoE are not mutually exclusive disorders and can co-exist in the same patient. If so, it is conceivable that GORD might cause or exacerbate EoE, in which case the effects of PPIs on gastric acid inhibition alone might be beneficial.

7. Regarding their series of 117 patients responders to PPIs misdiagnosed with EoE, we encourage the authors to submit their large series for peer review. A scientific debate should rely on peer reviewed data, not on unpublished series.

Collectively, our Position Paper underscores evolving facts and unsolved issues of PPI-REE. Further studies on PPI-REE in children are certainly warranted to improve our diagnostic and therapeutic strategy and clarify our knowledge on this intriguing and challenging disorder.

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