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Letter: PPI in EoE – more questions than answers. Authors' reply

EDITORS,

To relieve concerns about the validity of our results,[1,2] DSS has been used in several studies,[3-5] including one carried out by Miehlke,[6] because no validated instrument is available to assess symptoms in EoE patients in most European languages. DSS assesses frequency, intensity and duration of dysphagia; total scores range from 1 to 15. Clinical remission was defined as ≥50% reduction regarding baseline DSS.[3-5] Instead, Miehlke considered it as a decrease over 1/3 from baseline DSS.[6] The first component of DSS (dysphagia frequency) can only be scored 0 after 1 year of treatment. Because effectiveness of PPI therapy was assessed after 8-12 weeks, scores were highly influenced by baseline DSS. A complete remission ("0 dysphagia episodes during the last year") is achieved after 1 year of effective therapy, which is not meaningful in clinical practice,[7] thus it is difficult to achieve the minimum DSS after a short-term treatment. As DSS was not completed by ~1/3 of patients, a second point of clinical assessment is provided by physicians after the institution of a therapy for EoE, in order to capture short-term effectiveness of any intervention.

Histologic remission was defined as <15 eos/hpf at all oesophageal levels after therapy. This is a well-documented, reasonable endpoint in clinical settings that prospectively identifies most patients with symptomatic and endoscopic improvements.[8] Pushing the response threshold lower than <15 eos/hpf did not result in large gains of response. The FDA recommends stringent thresholds (<6 eos/hpf) for trials assessing drugs for EoE, but risk/benefit ratios of reducing response thresholds in practice need to be considered.

TABLE 1 Description of EoE patients with a single PPI treatment course registered in EOE CONNECT

	n	%
Clinical and histologic response to PPIs	115	61.8
Response to PPI not yet assessed at the time of interim analysis	35	18.8
No second therapy registered despite non-response to PPIs	36	19.4
Total	186	100

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Our paper's Table 1 refers to demographic and clinical characteristics of the cohort at the time of EoE diagnosis. The statement "symptom resolution with PPIs was actually 12.7%", is wrong. Instead, 12.7% of patients who completed the DSS at baseline had a score of 0-4 points (*ie* mild symptoms).

Per-protocol and intention-to-treat (ITT) analyses apply to clinical trials, but never to observational studies,[9] which invalidate calculations proposed by Miehlke. ITT analysis aims to reduce bias when not all patients assigned to an intervention actually receive it, or when it is unknown whether or not the outcome of interest occurred in some of the patients admitted to the study.[10] Because of the dynamic nature of a prospective registry such as EoE CONNECT, some patients were still receiving PPIs at the interim analysis. Considering these patients as lost to follow-up or unresponsive to PPIs would be completely wrong.

Supplementary Table 5 of our article provided details on the second treatment options among our 630 patients. Only 36 patients had no information recorded on the therapy used after PPIs (Table 1).

A clinical trial is the best design to compare efficacy and safety of PPIs vs other therapies for EoE, but we fear that such a trial will never be performed. Independent registries like EoE CONNECT can provide reliable data to inform the best decisions of physicians in environments of uncertainty and as many biased interests as that of EoE.

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The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]

LINKED CONTENT

This article is linked to Laserna-Mendieta et al and Miehlke et al papers. To view these articles, visit https://doi.org/10.1111/apt.15957 and https://doi.org/10.1111/apt.16194

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