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Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry

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Summary

Background: Proton pump inhibitors (PPIs) are the most commonly used first-line therapy for patients with eosinophilic oesophagitis (EoE). However, many aspects related to PPIs in EoE are still unknown.

Aims: To assess the effectiveness of PPI therapy for EoE in real-world practice.

Methods: This cross-sectional study collected data on PPI efficacy from the multicentre EoE CONNECT database. Clinical remission was defined as a decrease of ≥50% in dysphagia symptom score; histological remission was defined as a peak eosinophil count below 15 eosinophils per high-power field. Factors associated with effectiveness of PPI therapy were identified by binary logistic regression multivariate analyses.

Results: Overall, 630 patients (76 children) received PPI as initial therapy (n = 600) or after failure to respond to other therapies (n = 30). PPI therapy achieved eosinophil density below 15 eosinophils per high-power field in 48.8% and a decreased symptom score in 71.0% of patients. More EoE patients with an inflammatory rather than stricturing phenotype accomplished clinico-histological remission after PPI therapy (OR 3.7; 95% CI, 1.4-9.5); as well as those who prolonged treatment length from 8 to 12 weeks (OR 2.7; 95% CI, 1.3-5.3). After achieving clinico-histological remission of EoE, PPI dosage reduction was effectively maintained in 69.9% of patients, but tended to be less effective among those with a stricturing phenotype.

Conclusions: Inflammatory EoE phenotype and treatment duration up to 12 weeks correlated with greater chance for inducing remission of EoE. A stricturing phenotype decreased response rates to PPI therapy both initially and in the long term.

The complete list of authors' affiliation list are listed in Appendix 1.

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[Correction added on August 12, 2020, after first online publication: In the Results section of the Summary, "≥50% from baseline" was deleted from "...and a decreased symptom score ≥50% from baseline in 71.0% of patients." In the Conclusions section of the Summary, the first sentence was revised from "... up to 12 weeks provided the greatest benefits for inducing remission of EoE."]

1 | INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated inflammatory disease typically presenting with symptoms of oesophageal dysfunction and histologically characterised by a dense infiltration by eosinophils restricted to the oesophagus.[1] The natural history of EoE is defined by chronic or intermittent symptoms and persistence of inflammation over time,[2] which leads to oesophageal remodelling with collagen deposition, stricture formation and functional damage.[3,4] This fact, together with the impairment EoE produces on patients' health-related quality of life[5] indicates a need to treat symptomatic patients.

From being considered a refractory form of gastro-oesophageal reflux disease,[6] EoE was recognised early as a particular form of food allergy, triggered predominantly by food antigens,[7] and several modalities of dietary therapy demonstrated effectiveness in inducing disease remission.[8] In parallel, several trials showed that swallowed topic corticosteroids were also effective,[9,10] with oesophagus-targeted formulations providing better results.[11,12] Novel advanced therapies are being developed currently.[13] However, the aspect that has generated the most progress in the treatment of EoE in recent years is related to the use of proton pump inhibitors (PPIs).[14] Over the course of just a decade PPIs have gone from being an instrument to rule out gastro-oesophageal reflux disease as a cause of oesophageal eosinophilia,[15] to the defining factor of a new clinical entity called PPI-responsive oesophageal eosinophilia[16] and, finally, to constitute a true anti-inflammatory treatment for EoE.[1,17,18] The ability of PPIs to reduce both symptoms and eosinophilic infiltration in patients with EoE has been repeatedly documented.[19] The acid independent anti-inflammatory properties of PPIs were first demonstrated in EoE. PPI therapy significantly down-regulated oesophageal gene expression of *eotaxin-3/CCL26* and T helper-2 cytokines *interleukin (IL)-5* and *IL-3* in biopsies from patients with EoE. This was also witnessed in patients treated with swallowed topic corticosteroids,[20] and both drugs showed overlapping effects in reversing the changes in the allergic oesophageal transcriptome that characterise EoE.[21]

The ability of PPIs to rid a moderate proportion of patients with EoE of inflammation and symptoms through a cheap and, in general, safe drug has contributed to placing them as a first-line option for the treatment of EoE in patients of all ages, at the same level of swallowed topic steroids and elimination diets,[1] and has made PPIs the most frequently used initial treatment option in real clinical practice.[22] However, many of the aspects related to the efficacy of PPIs in EoE are still unknown, largely because all the evidence to date has been provided by observational studies, generally involving small numbers of patients.[23]

Through an analysis of EoE CONNECT, the largest multicentre registry of patients with EoE, this study aims to provide data on the efficacy of PPI treatment for EoE in actual clinical practice, and to help clarify some of the questions that remain regarding this anti-inflammatory treatment approach.

2 | PATIENTS AND METHODS

2.1 | Study protocol

This cross-sectional analysis focused on the "European Registry of Clinical, Environmental and Genetic Determinants in Eosinophilic Oesophagitis" (EoE CONNECT), an international multicentre prospective-maintained non-interventional registry that was started in 2016 and was promoted by United European Gastroenterology as a part of the Link Award program "Harmonizing diagnosis and therapy of Eosinophilic Oesophagitis across Europe (HaEoE-EU)". EoE CONNECT is managed by EUREOS, the European Society of EoE.[22]

Patients of all ages with a confirmed diagnosis of EoE, no previous PPI treatment but having received at least one therapeutic intervention based on a PPI drug as first- or second-line treatment and who had provided informed consent to be registered on the EoE CONNECT database were included in the present study. Prospective treatment data were registered sequentially, and new sequences were created each time a different treatment (active principle, formulation or dose) was administered to a patient. The EoE CONNECT registry was approved by Research Ethics Committees in all participating centres. All co-authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Data collection

Information is imputed onto EoE CONNECT by practitioners during face-to-face clinical appointments. Variables retrieved for this study included patients' demography, EoE characteristics at diagnosis (phenotype, dysphagia symptoms score and endoscopic findings), starting date of PPI therapy used for EoE (active principle, dose regimen and daily dose), clinical and histological response to therapy and evaluation date for PPI therapy. Endoscopic findings at baseline endoscopy were assessed by the EREFS scoring system[24]; rings and strictures were classified as fibrotic findings, while oedema, furrows and exudates were defined as inflammatory features.[25]

2.3 | Monitoring and quality data

The database was monitored and individual treatment data were manually revised to evaluate whether the study selection criteria were met, the information was correctly registered and ultimately, to ensure the correct order of therapies to guarantee the highest scientific and ethical standards. Data completion was assessed based on the following three pivotal group of variables: "baseline characteristics," "PPI treatment," and "effectiveness of results". Duplicates were removed; data discordances were resolved by querying the investigators and through group e-mailing. Additionally, after data extraction and prior to statistical analysis, the database was reviewed for inconsistencies and subsequently subjected to data cleaning.

2.4 | Definitions

2.4.1 | Active disease

Active disease was defined as a peak eosinophilic infiltrate by ≥15 cells per high power field (hpf) at any oesophageal level together with ≥5 points in the Dysphagia Symptoms Score, a nonvalidated measure instrument previously used in trials assessing drugs[26,27] and diets[28,29] involving adolescent and adult EoE patients. A Dysphagia Symptoms Score ≥8 was considered as severe dysphagia as previously described.[22] Subjective symptom intensity reported by either children or parents was considered for younger children.

2.4.2 | PPI doses

Standard doses of PPI included omeprazole 20 mg, pantoprazole 40mg, esomeprazole 20 mg, lansoprazole 30 mg and rabeprazole 20 mg daily, following the proposal of The World Health Organization Collaborating Centre for Drug Statistics Methodology regarding treatment of gastro-oesophageal reflux disease (http://www.whocc.no/atc_ddd_index/?code1/4A02BC&showdescription 1/4yes, accessed April 4, 2020), consensus guidelines[30] and experimental research.[21-33] Double doses or higher of the above were considered high-dose PPI,[34] and a low dose was defined when PPIs were given under standard or half-standard doses.

2.4.3 | Evaluation of response

Deep histological remission was defined as an eosinophil peak count of <5 eosinophils/hpf at all oesophageal levels after therapy; histological remission was considered as a peak count between 5 and 15 eosinophils/hpf.

Symptomatic improvement was independently assessed by changes in Dysphagia Symptoms Score reported by patients and by clinicians' perceptions. A decrease of more than 50% in baseline Dysphagia Symptoms Score after therapy was considered clinical remission in older children and adults, as previously defined[22,28,29]; a symptomatic improvement ≤50% from baseline was considered as clinical response. For younger children, any subjective improvement in symptoms reported by either children or parents was considered as clinical remission. In addition, clinicians semi-quantitatively scored changes in symptoms from the initiation of therapy as complete clinical remission, partial remission or no response.

Clinico-histological remission was defined as the simultaneous combination of symptomatic remission or improvement and all degrees of histological remission (peak eosinophil count <15 eosinophils per hpf) in the same patient after therapy.

Lack of efficacy was defined either as maintenance or worsening of patient's symptoms combined with persistence of histological activity of the disease at the end of PPI therapy, or a situation that led the physician to escalate the dose of PPI or change to an alternative drug or diet.

2.5 | Statistical analysis

Means and SDs, or alternatively medians and interquartile ranges (IQR), were reported for continuous variables and proportions for categorical data. Frequency tables were generated for treatment use and effectiveness. Contingency tables to assess demographical and clinical factors influencing treatment response rates were produced and analysed by chi-square or Fisher exact (univariate) test. A binary logistic multivariate regression analysis was performed to assess the overall effect of PPI treatment over variables identified in univariate analyses. All analyses were carried out using PASW 18.0 statistical analysis software (SPSS Inc). Statistical significance was considered when $P < 0.05$. Odd ratio (OR) was reported for those variables reaching statistical significance.

3 | RESULTS

3.1 | Study population

On the search date, January 30, 2020, 842 patients were registered on EoE CONNECT as having demographical data completed. Of those, 630 had PPI as an induction treatment, either as first-line therapy (n = 600) or as second-line therapy after failure of other treatments (n = 30). Among these 630 patients, PPI therapy was subsequently used to maintain remission in 172 of them either by modifying the dose or changing the PPI drug. Maintenance therapy with a reduced dose of PPI was prescribed in 138 of the 172 patients.

Patients were recruited at 13 hospitals in Spain, Italy and Denmark. Table 1 summarises the main demographic and clinical characteristics of the EoE patients included in this study.

3.2 | PPIs as initial therapy to induce remission in EoE

First-line treatment including PPIs alone or in combination represented 83.6% of all initial therapies for patients with EoE registered on EoE CONNECT. Six-hundred patients (94.3%) received PPI therapy alone and 25 (3.9%) used it in association with swallowed topic corticosteroids. PPIs were rarely associated with diets or dilation as the initial option to treat EoE (Table S1). Additionally, PPI monotherapy was prescribed as second-line therapy in 30 patients who failed dietary treatments (n = 15), swallowed topic corticosteroids (n = 14) and systemic steroids (n = 1). Subsequent descriptive data and analyses for effectiveness were related exclusively to the 630 patients receiving PPIs alone to induce remission of EoE.

Omeprazole was the most commonly prescribed first-line PPI in patients with EoE (48.4%), while rabeprazole was the least prescribed option (4.0%) (Table S2). Double doses (ie omeprazole 40 mg daily and equivalent) or higher were used in the vast majority of cases (87.1%), either split as a twice daily dose (97.4%) or as a once daily intake (2.6%). While the daily dosages for the most prescribed drugs of omeprazole (40 mg), pantoprazole (80 mg) and lansoprazole (60 mg) were double, esomeprazole was most frequently prescribed as a quadruple dosage (80 mg; in 74.0% of EoE patients receiving esomeprazole).

TABLE 1 Demographic and clinical characteristics of the patients treated with proton pump inhibitors alone as therapy for induction or maintenance of remission in eosinophilic oesophagitis. In maintenance therapy, only patients with dosage reduction were included

	Induction	Maintenance
Number of patients	630	138
Male, n (%)	473 (75.1)	103 (74.6)
Mean age (SD), years	35.4 (14.1)	38.9 (14.4)
Children, n (%)	76 (12.2)	11 (8.0)
Country of origin, n (%)		
Spain	544 (86.3)	131 (94.9)
Italy	75 (11.9)	6 (4.4)
Denmark	11 (1.8)	1 (0.7)
Phenotype at diagnosis, n (%)		
Inflammatory[a]	426 (76.3)	106 (84.8)
Mixed[a]	84 (15.1)	12 (9.6)
Stricturing[a]	48 (8.6)	7 (5.6)
No data[b]	72 (11.4)	13 (9.4)
Dysphagia symptoms score, n (%)		
0-4 points[a]	52 (12.7)	8 (8.3)
5-15 points[a]	357 (87.3)	88 (91.7)
No data[b]	221 (35.1)	42 (30.4)
Endoscopic signs of fibrosis, n (%)[c]		
Yes[a]	316 (62.5)	69 (60.5)
No[a]	190 (37.5)	45 (39.5)
No data[b]	124 (19.7)	24 (17.4)

Note: Patients under 18 year-old were considered children.
Abbreviations: n, number of patients; SD, standard deviation.
[a]Percentages are calculated over the total number of patients with information available.
[b]Percentages calculated over the full series of patients.
[c]These included rings and strictures

The median and IQR duration of PPI therapy up to evaluation was 72 (62-98) days. As shown in Table 2, most patients (37.8%) were treated between 56 and 70 days (ie 8 to 10 weeks), in agreement with the recommendation of clinical practice guidelines of a minimum of 8 weeks PPI treatment before endoscopic evaluation.[1,35] A minority of patients (10.5%) were evaluated before the 8th week or beyond the 6th month (5.0%). The remaining patients had PPI effectiveness evaluated between 71 and 180 days (10-26 weeks), including 19.9% for > 10 to 12 weeks and 26.8% within 3-6 months.

3.3 | Effectiveness of PPI therapy to induce remission in EoE

Overall, PPI therapy reduced eosinophil density below the diagnostic threshold of 15 eos/hpf in 48.8% of patients, with 37.9% of patients achieving deep histological remission. A further decrease in eosinophil count from baseline was documented in 4.1% of patients despite no histological remission. Regarding clinical response, PPI therapy induced symptomatic improvement in 71.0% of patients (Figure 1 and Table S3). When both responses were considered together, clinico-histological remission was achieved in 48.9% of the 569 patients who were fully evaluated.

Effectiveness rates of PPI induction therapy depended on the PPI dosages prescribed. Histological remission rate was higher for patients treated with high compared to standard or low doses (50.7% vs 36.7%; $P = 0.038$; OR = 1.77), and the same happened for symptomatic improvement (73.9% vs 54.6%; $P < 0.001$; OR = 2.36). Overall, the likelihood of achieving clinico-histological

TABLE 2 Effectiveness rates of proton pump inhibitor treatment to induce and maintain remission of eosinophilic oesophagitis (EoE), according to the duration of treatment from onset to clinical and histological evaluation. Only patients treated with proton pump inhibitors as single therapy for EoE were included. In maintenance therapy, only patients with dosage reduction were included

	Induction of remission			Maintenance		
	n	Prescriptions (%)	Effectiveness (%)	n	Prescriptions (%)	Effectiveness (%)
≤55 days	38	10.5	47.1	3	3.3	50.0
56-70 days	137	37.8	50.4	11	12.2	87.5
71-90 days	72	19.9	65.2	14	15.6	66.7
91-180 days	97	26.8	43.6	30	33.3	55.2
≥181 days	18	5.0	47.1	32	35.6	69.0
No data	268	–	–	48	–	–
Total	630	100	–	138	100	–

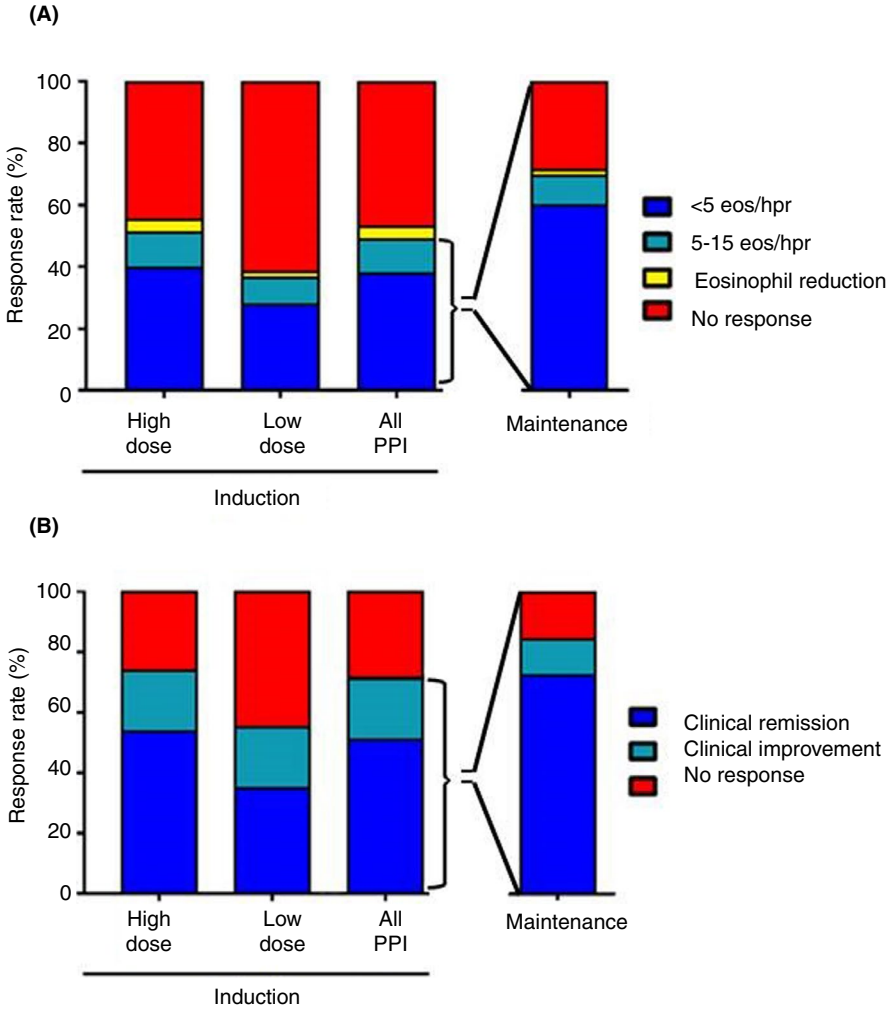

FIGURE 1 Bar chart for histological (A) and symptomatic (B) responses for proton pump inhibitor (PPI) mono-therapy to induce and maintain remission in patients with eosinophilic oesophagitis. For induction of remission, patients were classified according to the PPI dosage prescribed: high dose was double dosage or higher, and low dose was standard dosage or lower. For maintenance therapy, only patients with dosage reduction from that used for induction were included. eos/hpf: eosinophils per high power field

remission was greater for high compared to standard or low PPI doses (50.8% vs 35.8%, respectively; $P = 0.027$; OR = 1.85).

Among patients with high PPI doses, a greater proportion of them responded to quadruple (58.1%; n = 105) than to double doses (49.2%; n = 390), although this difference did not reach statistical significance ($P = 0.124$).

No significant differences were found among the different PPI drugs in achieving clinico-histological remission when used at high doses ($P = 0.091$). However, esomeprazole and omeprazole tended to provide higher effectiveness (55.8% and 54.5%, respectively) compared to pantoprazole, rabeprazole and lansoprazole (46.3%, 38.9% and 37.0%, respectively) (Table S4). This trend to a higher effectiveness for esomeprazole and omeprazole in clinico-histological response was not due to use of quadruple doses among these patients, since patients with double doses displayed similar response ratios (57.1% and 53.5%, respectively).

PPI therapy was significantly less effective in inducing clinico-histological remission when it was prescribed after failure of a first-line therapy with diet or swallowed topic corticosteroids, compared with being used as the initial therapy for EoE (27.6% vs 50.0%, respectively; $P = 0.022$; OR = 2.6). The reduced number of patients evaluated in this sub-group (n = 29) means this difference should be interpreted cautiously, as it could also be identifying a subgroup of patients with low adherence to any therapy.

Finally, we assessed whether PPI treatment length influenced the effectiveness of achieving clinico-histological remission of EoE. An 8 to 10-week (56-0 days) PPI treatment length provided 50.4% remission rate, which increased to 65.2% when treatment was prolonged to between 71 and 90 days (>10 to 12 weeks). However, treating patients with PPI beyond the 3rd month (>90 days) decreased effectiveness to 44.1%, possibly because longer treatments might reduce adherence (Table 2). When effectiveness was compared among these three groups of patients, statistical significance was detected ($P = 0.022$).

3.4 | PPI therapy to maintain EoE in remission

In total, 172 patients who were amongst those who had received PPIs as induction therapy were also treated with PPIs to maintain remission of their disease (Table S5). Maintenance treatment strategies consisted of reducing the PPI dose in 138 patients, increasing the PPI dose in 20 patients, and switching to equivalent dosage of a different PPI drug in 14 patients. The remaining

patients, mostly those not responding to PPIs, were treated with dietary interventions (149 patients), STC (92 patients) and a combination of therapies involving PPIs (31 patients). Subsequent descriptive data and analyses for effectiveness refer exclusively to the 138 patients who received reduced PPI doses as single therapy to maintain EoE in remission.

Among PPI-responsive EoE patients, the most and the least prescribed drugs were omeprazole (58.7%) and rabeprazole (4.3%), respectively, which was also the case in induction of remission therapy (Table S2). Standard PPI doses were preferred to maintain EoE in remission (110 patients, 79.7%), while high PPI doses were still used in 21 patients (15.2%). The remaining 7 patients (5.1%) used half the standard doses.

Accurate data on effectiveness and evaluation date of PPI therapy to maintain EoE in remission was available for 90 patients (Table 2), assessed after a median of 117 days (IQR: 90-207) at the treatment institution.

3.5 | Effectiveness of PPI therapy to maintain EoE in remission

A reduced dose of PPI from that used for induction was effective in maintaining remission of EoE in 72 patients (69.2%), with 62 of them (59.6%) being in deep histological remission. As for symptoms, 98 patients (84.5%) reported any clinical improvement from baseline, with 84 of these patients (72.4%) being in clinical remission (Figure 1 and Table S3). Taken together, PPI therapy was effective in maintaining EoE in clinico-histological remission in 72 of the 103 (69.9%) patients who had both responses fully assessed.

As with induction therapy, PPI dose, drug type and length of treatment were analysed to identify potential differences in effectiveness, with no significant associations being found. The limited number of patients within subgroups however could have prevented identifying differences. In this sense, the clinico-histological maintenance of remission rates among patients who used quadruple doses of induction and switched to double doses for maintenance (n = 15) was 80%, while it was 68.2% among patients who received standard doses or lower for maintenance of remission (n = 88).

No PPI drug was found to be significantly superior to any other in maintaining EoE in remission when used at standard doses or lower. However, lansoprazole tended to be the least effective drug in terms of clinico-histological remission (57.1%) (Table S4). As for treatment length, effectiveness was higher when assessed after 2-3 months (75%), than when it was done between 3 and 6 months (55.2%) or beyond the 6th month (69.0%) (Table 2).

Finally, the effectiveness of PPIs to maintain EoE in clinico-histological remission tended to be related to their effectiveness to induce disease remission, which was greater when deep remission (<5 eosinophils per hpf) was reached (n = 83) than when eosinophil count reduction was between 6 and 15 eosinophils per hpf (n = 14) after induction treatment (73.5% vs 50.0%; $P = 0.112$).

3.6 | Determinants for PPI therapy effectiveness in inducing EoE remission

In order to identify demographic and clinical variables associated with the effectiveness of PPI therapy to induce and maintain clinico-histological remission of EoE, uni- and multivariate analyses were performed. The variables and the categories compared are described in Table S6.

Apart from PPI dose and treatment length, EoE phenotype and presence of fibrotic changes at baseline endoscopy (rings and/or strictures) were identified as being significantly associated with effectiveness of PPI to induce clinico-histological remission of EoE. A multivariate analysis was performed with data from the 257 patients who had been assessed for all the four variables. EoE phenotype and treatment length remained statistically significant, providing evidence that patients with an inflammatory instead of stricturing phenotype had higher chances of accomplishing clinico-histological remission of EoE after PPI therapy (OR 3.7; 95% CI, 1.4-9.5); and a length of PPI treatment between 71 and 90 days provided significantly higher remission rates than that which lasted between 56 and 70 days (OR 2.7; 95% CI, 1.3-5.3) (Table 3).

Regarding PPI therapy in maintaining EoE remission, no variable was found to be significant for clinico-histological effectiveness in univariate analysis, although phenotype was close to statistical significance, with PPI therapy showing more than twice the effectiveness in inflammatory compared to stricturing phenotype (Table S7).

In addition, although no statistical differences in effectiveness were detected between children and adults, an increased clinico-histological response rate was observed for adults for both induction and maintenance therapies with PPIs (Table S7).

4 | DISCUSSION

PPIs are currently considered a first-line anti-inflammatory therapy for induction and maintenance of remission in patients with EoE of all ages, together with swallowed topic corticosteroids and dietary therapy.[1] In this study we have reported the largest series to date in assessing the effectiveness of PPI in EoE according to data obtained from real-world clinical practice.

Our results showed that PPI therapy for histological remission of EoE was accomplished in 48.8% of patients of all ages, while 71% report some improvement in symptoms, closely reproducing the results already provided by previous research, most of which have been summarised in a prior meta-analysis.[19] For the first time we can provide data on the combined efficacy of PPIs in achieving clinical and histological remission of EoE together, at 48.9%, allowing us to compare this with alternative drug or diet-based therapies for EoE.

Furthermore, our study provides new data, in that PPI treatment is more effective in achieving clinico-histological remission of the disease when used in higher instead of standard or lower doses (50.8% vs 35.8%), and when the duration of therapy is prolonged from 8 to 12 weeks (50.4% vs. 65.2%). Parallel results have been recently reported for diet[35] and swallowed topic corticosteroids,[11] for which

TABLE 3 Uni- and multi-variate statistical analyses of those variables that significantly determined the effectiveness of proton-pump inhibitor therapy to induce clinico-histological remission in patients with eosinophilic oesophagitis

	Induction therapy					
Variable	n (univariate)	Clinic-histological remission (% of patients)	*P* (univariate)	n (multivariate)	*P* (multivariate)	OR (95% CI)
EoE phenotype						
Inflammatory	386	50.3	0.011	215	0.007	3.7 (1.4-9.5)
Mixed	75	46.7		16	Non-significant	—
Stricturing	45	26.7		26	Reference category	—
Fibrotic features at baseline endoscopy						
Yes	284	43.0	0.016	164	Non-significant	—
No	173	54.9		93		—
Proton pump inhibitor dose						
High	498	50.8	0.027	238	Non-significant	—
Low	67	35.8		19		—
Treatment length until evaluation (days)						
56-70	133	50.4	0.022	112	Reference category	—
71-90	69	65.2		58	0.006	2.7 (1.3-5.3)
≥91	111	44.1		87	Non-significant	—

Note: CI, confidence interval; n, number of patients with both clinical and histological responses assessed; OR, odds ratio in multivariate analysis; *P*, *P*-value.

increased effectiveness rates were demonstrated when treatment length was extended from 6 to 12 weeks. However, prolonging treatment duration for this period was associated with lower remission rates, most probably related to a reduced adherence to therapy.

Our results also document for the first time that PPI therapy was significantly less effective among patients with a stricturing phenotype or those who exhibited strictures or rings at endoscopy; these should be considered a priori for treatment with more effective anti-inflammatory alternatives, such as swallowed topic corticosteroids. The potential of swallowed topic corticosteroids to reverse the phenomena associated with fibrous remodelling of the oesophagus has begun to be revealed,[4,36,37] but we still do not have information on the ability of PPIs to reverse this process, which takes place mainly in the subepithelial layers and which is evaluated in a limited way by endoscopic biopsies. EoE represents a transmural disease,[38] in which eosinophils and mast cells that infiltrate the subepithelial layers of the oesophagus lead to fibrous remodelling with collagen deposition.[39] Omeprazole has been documented to block signal transducer and activator of transcription 6 from binding to the *eotaxin-3* gene promoter in oesophageal epithelial cells, thereby preventing T helper-2 cytokines from stimulating *eotaxin-3* expression,[17,40] this anti-inflammatory effect being entirely independent of its effects on gastric acid secretion. In contrast, omeprazole does not inhibit T helper-2 cytokine-stimulated *eotaxin-3* expression by oesophageal fibroblasts,[18] suggesting that PPIs would have limited impact on subepithelial EoE processes such as fibrosis. Since we could not assess changes in endoscopic features over the period of PPI therapy due to the limited information on this matter, findings on the lack of effect of PPI on fibrous remodelling in EoE were not validated in our research.

We have also documented that the different PPI drugs did not show statistically significant differences in terms of their efficacy in inducing remission of EoE when used at equivalent doses, despite lansoprazole tending to be the least effective. However, these results are influenced by the fact that lansoprazole, which is available as an orally disintegrating tablet, was more frequently prescribed to patients with stricturing phenotype than to those with inflammatory or mixed phenotypes (27.1% vs 12.0%). Furthermore, esomeprazole was the only PPI drug used more frequently at double doses than at standard doses to maintain remission, due it was used at quadruple doses for induction of remission in the majority of patients receiving this drug.

So far, only three studies with a limited number of patients with EoE have evaluated the efficacy of PPIs in maintaining the remission initially induced with the same drugs, including two in adult patients[41,42] and one more in children.[43] Half the doses of PPI as those that induced remission were used in all studies, which uniformly documented that standard doses of PPIs maintained histological remission of EoE in 83%-70% of patients, close to the 69.2% rate we documented. Stricturing phenotype patients again presented less likelihood in maintaining remission after PPI dose reduction.

The strengths of our study include the use of a large, multicentre series of patients with EoE, prospectively recruited from multiple sites in three different countries. The active monitoring of data ensured reliability of the registered information. Our results reflect actual clinical practice and provide more representative data than those derived from protocolised studies. At the same time, this fact also represents the greatest limitation of our study, because patients were not managed under pre-defined dose or treatment schedules, but according to the variable

criteria followed by the different contributors. The design of our study prevents comparing the effectiveness of PPIs with other treatment modalities, and therefore does not allow positioning this treatment over other alternatives, such as topical swallowed corticosteroids or elimination diets.[44] However, we provide here a strong hint that IBPs are effective in managing EoE. Future randomised studies should better define the comparative effectiveness of the different therapies for EoE. Only a minority of patients (~10%) were under 18 years old, and despite them showing no differences with adults for the major outcomes, the external validity of our results for paediatric populations are limited. As the majority of the recruiters were gastroenterologists attending adult patients, we could not compare potential differences in patient management with regard to paediatricians, allergists and providers of other specialties. In addition, our study focused exclusively on the effectiveness of PPI used as single therapy for EoE, so the potential benefit of associating this drug with swallowed topic corticosteroids, diets or even endoscopic dilation was not assessed. Finally, the reduced number of patients with assessment of effectiveness of PPI as maintenance therapy compared to those we evaluated for induction for remission might have limited subgroup comparisons, thus preventing us from finding determinants for effectiveness with statistical significance.

In conclusion, we provide evidence that high PPI doses are an effective anti-inflammatory therapy that achieves histological and clinical remission in half of the patients with EoE, with around 70% of responding patients being able to maintain long term remission after dose reduction. All PPI drugs were similarly effective, with high doses used for 10-12 weeks providing the highest benefit for induction of remission. Patients with stricturing EoE were less likely to respond to PPI therapy initially and in the long term, so they should be considered candidates for alternative anti-inflammatory options.

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AUTHORSHIP

Guarantor of the article: Alfredo J Lucendo

Author contributions: Emilio J Laserna-Mendieta, Ángel Arias, and Alfredo J Lucendo were involved with the study design, data collection, data analysis, data interpretation, and manuscript writing. Sergio Casabona, Danila Guagnozzi, Edoardo Savarino, Antonia Perelló, Antonio Guardiola, Jesús Barrio, Isabel Pérez-Martínez, Anne Lund Krarup, Javier Alcedo, Susana de la Riva, Esther Rey-Iborra, and Cecilio Santander participated in the collection and interpretation of data. All authors provided a critical review and relevant intellectual content to the manuscript and approved its final version

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX 1

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