Long-term Treatment With Proton Pump Inhibitors Is Effective in Children With Eosinophilic Esophagitis

*Carolina Gutiérrez-Junquera, †Sonia Fernández-Fernández, *M. Luz Cilleruelo, †Ana Rayo, ‡Luis Echeverría, †Belén Borrell, and *Enriqueta Román

See ''A New Paradigm in the Treatment of Eosinophilic Esophagitis: Proton Pump Inhibitors Are Safe, Aim for ''Deep Remission'' '' by Ellison and Philpott on page 146.

ABSTRACT

Objectives: Proton pump inhibitor (PPI)-responsive eosinophilic esophagitis (EoE) is frequently observed in children, but data on long-term treatment are scarce. The objective of this study is to evaluate the long-term efficacy and safety of PPIs in children with EoE.

Methods: This prospective study enrolled children with EoE and histological remission to an 8-week esomeprazole trial (1 mg/kg/dose, twice daily). Esomeprazole was maintained at 1 mg/kg/day for 1 year. Symptom recurrence and adverse events were monitored and a follow-up endoscopy was performed at 12 months. Complete histological remission was defined as $\leq$5 eosinophils/high-power field (eos/hpf), and partial histological remission as $>$5 and $<$15 eos/hpf. Patients had no concomitant dietary restrictions or topical steroid.

Results: Fifty-seven children were included. Histological remission on maintenance PPI therapy was present in 40 children (70.1%; 95% CI 56.5–81.5). Long-term remission rate was higher in children with initial complete histological remission than in those with partial remission (81% vs 50%, $P = 0.014$). Forty-nine children (86%) remained asymptomatic. Pretreatment clinical and histological findings and median PPI dose/kg/day were similar between relapsers and nonrelapsers. Eleven out of 12 children (91.6%) receiving esomeprazole 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 12 additional months remained in remission. Mild and transient side effects without requiring PPI avoidance were observed in 5 children.

Conclusions: Up to 70% of children with PPI-responsive EoE remain in histological and clinical remission on a low-dose maintenance treatment at 1-year follow-up, with adequate safety profile. Complete histological remission to an 8-week PPI trial was associated with higher probability of histological remission on maintenance therapy.

Key Words: adolescents, children, efficacy, eosinophilic esophagitis, long-term safety, proton pump inhibitors

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From the *Pediatric Gastroenterology Unit, Department of Pediatrics, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, the †Pediatric Gastroenterology Unit, Department of Pediatrics, Hospital Universitario Severo Ochoa, Leganés, and the ‡Pediatric Allergy Unit, Department of Pediatrics, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain.

Address correspondence and reprint requests to Carolina Gutiérrez-Junquera, PhD, Pediatric Gastroenterology Unit, Department of Pediatrics, Hospital Universitario Puerta de Hierro-Majadahonda, Calle Manuel de Falla 1, 28220 Majadahonda, Madrid, Spain (e-mail: carolina.gutijun@salud.madrid.org).

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What Is Known

- Almost 60% of children with eosinophilic esophagitis respond to high-dose proton pump inhibitor induction treatment.
- Small case series have suggested that proton pump inhibitor responsiveness in children with eosinophilic esophagitis is a transient phenomenon.
- Studies in adults with proton pump inhibitor-responsive eosinophilic esophagitis have shown that 70 to 80% present histological remission on maintenance treatment.

What Is New

- Proton pump inhibitor responsiveness is not a transient phenomenon in children with eosinophilic esophagitis. Around 70% of children on a low proton pump inhibitor dose maintain histological remission after 1 year of treatment.
- Complete histological remission to an 8-week proton pump inhibitor trial was associated with a higher probability of histological remission on maintenance treatment.

Eosinophilic esophagitis (EoE) is an emerging disease in children in Western countries with a significant increase in its incidence since 2008 (1). Nowadays, EoE is one of the most prevalent esophageal diseases and is the leading cause of dysphagia and food impaction in children.

EoE is a chronic disorder characterized by esophageal dysfunction and eosinophil-predominant inflammation confined to the esophagus. Diagnosis criteria established in 2011 included the persistence of $\geq$15 eosinophil (eos)/high-power field (hpf) after a PPI trial in order to exclude gastroesophageal reflux disease (GERD) and PPI-responsive esophageal eosinophilia (PPI-REE) (2). This latter disorder refers to patients with EoE phenotype and esophageal eosinophilia, which respond to PPI treatment.

A recent systematic review and meta-analysis showed that around 50% of adults and children with esophageal eosinophilia respond to PPI (3). In a prospective study, we observed that 68% of children with esophageal eosinophilia and esophageal dysfunction presented histological remission with an 8-week PPI trial (4).

Over the past few years, evolving evidence has emerged that PPI-REE has similar characteristics to those of EoE at clinical, endoscopic, histological, molecular, and genetic levels, which are very different from those of GERD (5). In 2017, this was incorporated into a new definition of EoE as a chronic, local immune-mediated esophageal disease characterized by symptoms related to esophageal

dysfunction and eosinophil-predominant inflammation (6). A PPI trial is not needed, and PPI should be considered as another treatment as swallowed steroids or elimination diets.

Chronicity is the main characteristic of EoE, so maintenance treatment is important. Nevertheless, there are scarce efficacy data on long-term PPI treatment in EoE. Clinical-histological recurrence was reported in 2 retrospective series of children with EoE under maintenance PPI treatment (7,8). On the contrary, data from 2 studies in adults with EoE showed that between 73% and 81% of patients stay in remission with long-term, low-dose PPI treatment (9,10).

Although PPI are considered safe drugs, recent concerns about possible adverse events have appeared mainly in adults (11). Data on the safety of chronic PPI use in children are scarce (12).

We conducted a prospective study to evaluate the efficacy and safety of long-term PPI treatment in children with EoE.

METHODS

This was a prospective study conducted at 2 pediatric hospitals in Madrid between February 2013 and August 2017. We included consecutive children from 1 month to 15 years of age who fulfilled criteria for EoE diagnosis according to the recently published evidence-based European guidelines (6) and presented remission to an 8-week esomeprazole trial. Patients were newly diagnosed with EoE; the results of the initial 8-week esomeprazole trial were previously published (4).

The study was conducted according to the Declaration of Helsinki. All patients or parents gave their consent to participate in the study. Approvals from the Ethics Committee at the Hospital Universitario Puerta de Hierro-Majadahonda and Hospital Universitario Severo Ochoa were obtained.

Inclusion criteria were:

(1) At least one esophageal dysfunction symptom such as heartburn, chest pain, food impaction, abdominal pain, vomiting, regurgitation, dysphagia, and feeding difficulties and;
(2) Esophageal eosinophilia, defined as the presence of $\geq$15 eos/hpf (peak value) in 1 or more biopsy samples and;
(3) Histological remission to an 8-week esomeprazole trial, defined as $<$15 eos/hpf.

Children were excluded if they were receiving concomitant treatment with swallowed or oral steroids and/or elimination diet or had eosinophilic gastroenteritis.

Study Design

Children with esophageal symptoms underwent basal upper gastrointestinal endoscopy with biopsy sampling. Treatment with esomeprazole ($1\,mg \cdot kg^{-1} \cdot dose^{-1}$ twice a day, maximum dose 40 mg twice a day) was initiated for 8 weeks and a second upper endoscopy with esophageal biopsies was performed while on-treatment.

Responders continued on PPI treatment at a maintenance dose (esomeprazole $1 \cdot kg^{-1} \cdot dose^{-1}$ once a day, maximum dose 40 mg once a day). Clinical follow-up was performed every 3 months, and possible adverse effects, clinical outcomes, and adherence to treatment were recorded. Endoscopy was performed at the time of clinical recurrence, worsening of symptoms, or at 1 year from diagnosis in cases where patients remained asymptomatic.

Clinical and Laboratory Data

Baseline clinical and demographic data were recorded, including personal and familial history of allergy and previous treatment with food oral immunotherapy (OIT). An absolute blood eosinophil count was also recorded.

Symptoms were registered at baseline, after the 8-week PPI trial, regularly at each 3-month follow-up, and at the 12-month follow-up. Patients or parents were asked to score the symptoms on a written scale as ''complete resolution,'' ''clinical improvement,'' or ''no change in symptoms.''

Adverse events (headache, rash, episodes of acute gastroenteritis, diarrhea caused by *Clostridium difficile*, and pneumonia) were specifically asked and recorded in each clinical visit.

Laboratory tests (iron, ferritin, calcium, magnesium, and vitamin B12 levels) were performed at the 12-month follow-up.

Endoscopy and Histology

A gastrointestinal endoscopy was performed and the endoscopic signs were recorded and classified according to the Endoscopic Reference Score (EREFS) proposed and validated by Hirano et al (13). In addition, the presence of esophageal erosions or ulcers and esophageal fungal infection were also recorded.

Biopsy samples were obtained from the esophagus (at least 2 from the distal esophagus and 2 from upper mid esophagus). The maximum number of esophageal eosinophils was counted in a single high-power field corresponding to an area of $0.24\,mm^2$.

Definition of Histological Remission

Complete remission to PPI therapy was defined as $\leq$5 eos/hpf on all of the esophageal biopsy samples. Partial remission to PPI treatment was defined as $>$5 and $<$15 eos/hpf on any esophageal biopsy sample. Histological relapse was defined as $\geq$15 eos/hpf on any esophageal biopsy sample.

Endpoints

The main endpoint of the study was to assess the percentage of children on PPI maintenance treatment with histological remission at the 12-month follow-up.

Secondary endpoints were to evaluate predictive factors of sustained histological remission, clinical outcome on PPI maintenance treatment, and frequency of clinical or laboratory test-related adverse events.

Statistical Analysis

A descriptive analysis has been performed by means of absolute and relative frequencies for categorical variables and mean (standard deviation), or median (percentiles 25 and 75), as well as minimum and maximum values for quantitative variables.

A univariate analysis was performed using the chi-square or Fisher exact tests for categorical variables and Mann-Whitney test for quantitative ones. The significance level was established at 0.05, although Bonferroni correction was applied for multiple comparisons. Stata/IC v.15.1. software was used (StataCorp. 2017, Stata Statistical Software: Release 15, StataCorp LLC, College Station, TX).

RESULTS

One hundred and nine children with esophageal symptoms and EoE received an initial 8-week PPI treatment with esomeprazole ($1\,mg \cdot kg^{-1} \cdot dose^{-1}$ twice a day), and 72 (66%) showed histological remission.

Maintenance treatment with esomeprazole ($1\,mg \cdot kg^{-1} \cdot dose^{-1}$ once a day) was offered after the 8-week PPI trial. Sixty children completed a follow-up period of at least 12 months. Two

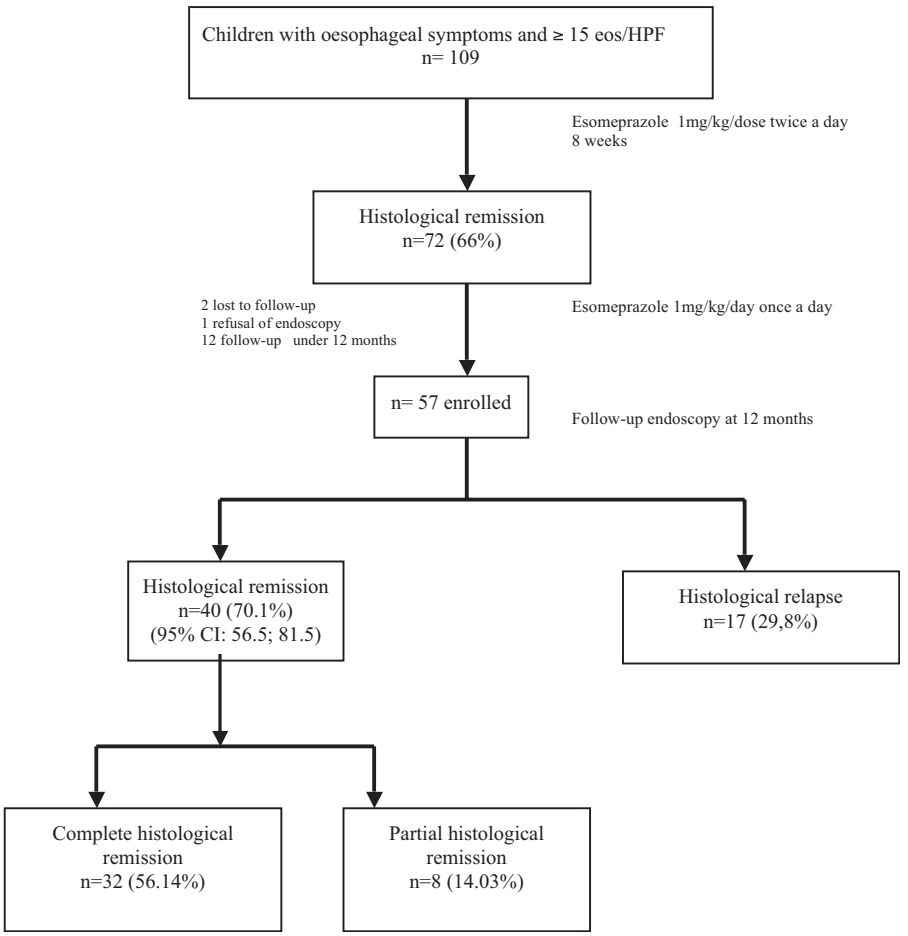

FIGURE 1. Flow chart of patients included in the study. Eos = eosinophil count; hpf = high power-field; PPI, proton pump inhibitor.

patients were lost to follow-up and 1 patient was not included because of parental refusal to perform a new endoscopy. As a result, 57 children (73.7% boys, median age 11 years, range 1–15 years) enrolled in the study (Fig. 1).

A follow-up endoscopy was performed at a median time of 14.5 months (p25; p75: 12.1; 15.6 months). Histological remission on maintenance treatment was present in 40 children (70.1%; 95% CI 56.5–81.5), complete remission ($\leq$5 eos/hpf) in 32, and partial remission (>5 and <15 eos/hpf) in 8 patients (Fig. 1).

Regarding the clinical outcome at 12 months, 49 (86%) children were asymptomatic, 3 (5.3%) had mild symptoms, and 5 patients (8.8%) had unchanged symptoms. A 14-month old infant presented an episode of choking at 8 months into the maintenance treatment; esophageal biopsy performed at that time showed complete histological remission.

Baseline pretreatment clinical data from patients with long-term histological remission and those with histological relapse are shown in Table 1. There were no significant differences in terms of age, sex, family, and personal history of atopy. The main clinical symptoms at the time of the first endoscopy were abdominal pain (59.65%), dysphagia (40.3%), vomiting (33.3%), and food impaction (28%), with no differences between both groups. The maintenance PPI dose was similar between patients with sustained histological remission and those who lost remission (median (p25; p75): 0.9 (0.77; 1.06) mg/kg/day versus 0.9 (0.8; 1.08) mg/kg/day, $P = 0.9$). The median pre-treatment peripheral eosinophils count (cells $\times 10^9$/L) was higher in children who lost remission.

Four children had received specific OIT (2 for milk and 2 for egg proteins), because of severe IgE-mediated allergy. All 4 children showed histological remission on maintenance treatment at the 12-month follow-up with continued ingestion of the specific food.

Baseline pretreatment endoscopic-histological findings are summarized in Table 1. The most frequently reported findings on the baseline endoscopy were furrows (71.9%), exudates (66%), and oedema (61.4%), with no difference between patients with sustained histological remission and those with histological relapse. A 10-year-old boy with dysphagia and episodes of food impaction presented rings and a stricture in medium esophagus. Eosinophil counts were >80 in distal esophagus and >70 in medium esophagus. He had short- and long-term histological remission to PPI treatment with resolution of stricture.

The pretreatment EREFS and peak eosinophils count (both in distal and medium esophagus) were similar between patients with histological remission or relapse on maintenance treatment. The median ERFES on the follow-up endoscopy at 12 months was 0 (p25; p75: 0;1) in children with histological remission versus 2 (p25; p75: 1; 3) in children with loss of remission ($P < 0.001$).

Thirty-seven children presented complete histological remission ($\leq$ 5 eos/hpf) after an 8-week PPI trial and 30 of them (81%) showed long-term histological remission. On the contrary, of the 20 children with partial initial histological remission, only 10 (50%) maintained remission on the follow-up endoscopy ($P = 0.014$; Fig. 2). The median EREFS after the 8-week PPI treatment was

TABLE 1. Comparison of baseline characteristics between patients with sustained and lost long-term remission to proton pump inhibitor therapy

	Long-term histological remission (n = 40)	Histological relapse (n = 17)	*P* value
Median age at diagnosis, years (P25; P75)	11.1 (8.6; 12.8)	9.0 (5.5; 10.6)	0.07
Male	29 (69%)	11 (73.3%)	0.75
Family history			
Any sign of atopy*	28 (70%)	12 (70%)	0. 22
Personal history			
Any sign of atopy*	25 (62.5%)	10 (58.8%)	0.79
Food allergy	11 (27.5%)	8 (47%)	0.15
Asthma	12 (30%)	8 (47%)	0.21
Rhinoconjunctivitis	17 (42.5%)	6 (35.3%)	0.61
Atopic dermatitis	7 (17.5%)	4 (23.5%)	0.59
Presenting symptoms			
Heartburn	11 (27.5%)	3 (17.6%)	0.43
Chest pain	11 (27.5%)	3 (17.6%)	0.43
Food impaction	9 (22.5%)	7 (41.2%)	0.15
Abdominal pain	26 (65%)	8 (47%)	0.21
Vomiting/regurgitation	14 (35%)	5 (29.4%)	0.68
Dysphagia	14 (35%)	9 (52.9%)	0.21
Food refusal	13 (32.5%)	4 (23.5%)	0.49
Laboratory data			
Median peripheral eosinophils count, cells $\times 10^9$/L (P25; P75)	310 (230; 430)	405 (380; 580)	0.0048
Endoscopic findings			
Fixed rings	5 (12.5%)	0 (0%)	0.12
Exudates	24 (60%)	14 (82.3%)	0.10
Furrows	27 (67.5%)	14 (82.3%)	0.25
Edema	22 (55%)	13 (76.5%)	0.12
Stricture	1 (0.02%)	0 (0%)	0.51
Crepe paper oesophagus	1 (0.02%)	1 (0.06%)	0.52
Ulcers or erosions	2 (0.05%)	0 (0%)	0.34
Endoscopic Reference Score (EREFS) Median (P25; P75)	3 (1; 4)	3 (2; 3)	0.74
Eosinophil count†			
Distal oesophagus			
<50	23 (57.5%)	10 (58.8%)	0.92
>50	17 (42.5%)	7 (41.2%)	
Medium oesophagus			0.53
<50	25 (62.5%)	10 (58.8%)	
>50	15 (37.5%)	7 (41.2%)	
Maximum eosinophil count Median (P25; P75)†	39 (23; 80)	40 (30;70)	0.90

EoE = eosinophilic esophagitis; EREFS = Endoscopic Reference Score.
*Including previous history of food allergy, asthma, rhinoconjuntivitis, or atopic dermatitis.
†Eosinophils per high power field (hpf), for an hpf area of 0,24 mm^2.

0 (p25; p75: 0; 1) in patients with long-term histological remission versus 1 (p25; p75: 0;1) in patients with histological relapse ($P = 0.027$).

Adverse events on PPI maintenance treatment occurred in 5 children during high-dose induction treatment (Table 2). No cases of pneumonia or diarrhea caused by *Clostridium difficile* were reported. In 30 children, laboratory analyses were performed at 12 months of treatment. Two of them showed low levels of ferritin (<6 ng/mL) with normal hemoglobin levels. Esophageal candidiasis was not observed during the follow-up endoscopy in any of the cases.

Twelve children received esomeprazole at $0.5\,mg \cdot kg^{-1} \cdot day^{-1}$ for an additional 12-month period, with a follow-up endoscopy at the end of the second follow-up year. Histological remission at 2 years of treatment was present in 11 children (91.6%; 10 complete histological remission and 1 partial histological remission).

DISCUSSION

In this prospective study, we observed that 70% of children with PPI-responsive EoE showed sustained histological remission with maintenance half-dose treatment at 12 months of follow-up. Moreover, sustained histological remission was also observed in 11 out of 12 children in which the dose was tapered down to $0.5\,mg \cdot kg^{-1} \cdot day^{-1}$ for an additional year. These data show that PPI remission is not a transient phenomenon in children as initially reported. Dohil et al (7) described 4 children with initial remission to PPI that presented clinical-histological recurrence, despite continued PPI therapy for 5 to 17 months. Schroeder et al (8) reported

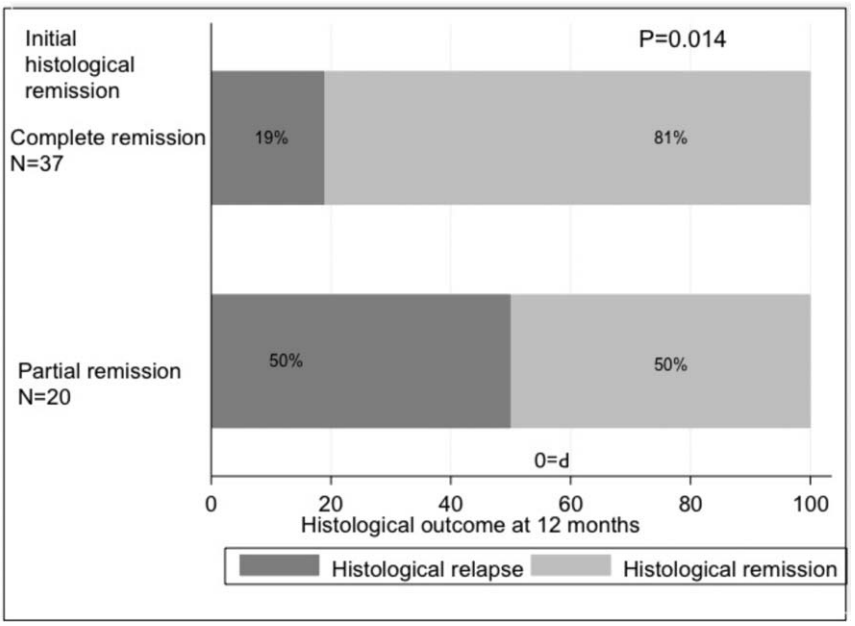

FIGURE 2. Comparison of long-term histological remission between patients with complete (≤ 5 eos/hpf) and partial (>5 and <15 eos/hpf) remission on the initial PPI trial. Eos = eosinophil count; hpf = high-power field.

another 2 children with clinical-histological relapse within 17 to 23 months, while receiving PPI therapy.

Our results in a large group of children corroborate what has been observed in adults. In a prospective study, Gómez Torrijos et al included adult patients with PPI-responsive EoE. They underwent a PPI taper down, observing that 31 of 38 patients (81%) remained in histological remission with omeprazole 40 mg once daily, as well as 15 of 18 patients (83%) who eventually tapered down to 20 mg once daily (10). Molina-Infante et al included 75 PPI-responsive EoE adult patients who had at least 12 months of follow-up in a multicenter retrospective study. PPI dose was tapered to the lowest dose that controlled symptoms, observing that 55 patients (73%) remained in histological remission at a mean follow-up of 26 months. In this latter study, 16 patients had stopped PPI treatment; 14 of them had symptom recurrence in the first year off PPI therapy. The other 2 patients remained asymptomatic, but histological recurrence was observed (9). These data emphasize that EoE is a chronic disease and clinical-histological recurrence occurs after treatment discontinuation, as observed with swallowed steroids (14).

Our study is relevant because it demonstrates a very good efficacy of long-term PPI treatment in pediatric EoE. Dietary therapy is an appealing maintenance treatment strategy in children with EoE because of the absence of adverse effects. Avoiding foods identified as triggers of EoE has been associated with very high rates of sustained histological remission in therapy-compliant adults (15,16). Philpott et al found a sustained remission rate >85% in adult patients at 3 months with all treatment modalities (budesonide, PPI, and elimination diet). At 9 months, only 10 of 18 patients on elimination diet (55%) were compliant and remained in remission (17). Therefore, diet elimination therapy does result in prolonged disease control, but compliance may be difficult. Studies on remission rate on long-term swallowed steroid treatment have shown conflicting results. A sustained histological remission rate of 58% was found in 54 children with topical fluticasone at the same initial dose (18). Topical budesonide at a maintenance dose of 0.5 mg/day in 28 adults was able to maintain esophageal eosinophilia <20 eos/hpf only in 50% of patients. A recent study from the same investigators with follow-up time up to 6 years observed that only 9.4% of 351 adults achieved long-lasting deep remission (clinical, endoscopic, and histological remission) (19).

We observed that clinical remission was more frequent than histological remission and 9 children who presented histological recurrence were asymptomatic. Only 1 child with histological remission showed clinical symptoms: an 8 months old infant with a choking episode, attributed to swallowing incoordination. It is already known that the correlation between clinical data and histological findings is poor in EoE (20,21). Therefore, histological analysis continues to be necessary for the diagnosis and monitoring of the disease.

TABLE 2. Adverse events reported among patients included in the present study

Age (years)	PPI	Dose (mg/kg/day)	Adverse event	Comments
8.3	Esomeprazole	1.1	Diarrhea	Resolved with no change in treatment
13.8	Esomeprazole	0.7	Diarrhea and abdominal pain	Resolved with no change in treatment
1.2	Esomeprazole	1.2	Diarrhea	Resolved with no change in treatment
10.5	Esomeprazole	2	Urticaria	Switch to lansoprazole, resolved
10.4	Esomeprazole	1.3	Headache	Switch to lansoprazole, resolved

PPI = proton-pump inhibitors.

We did not identify any baseline clinical or histological data, which could predict sustained remission to PPI. Baseline absolute blood eosinophils counts were higher in children who lost remission when compared to those with sustained remission. This could potentially reflect a more important allergic background (9) or a higher pretreatment eosinophilic infiltration in relapsers. However, both a personal history of atopy and peak eosinophil counts/hpf were similar in relapsers and nonrelapsers. Analysis of absolute blood eosinophil counts allows EoE patients to be differentiated from controls and can be correlated to histological activity in treated EoE patients, suggesting a potential role in EoE disease activity monitoring (22–24), but not as a predictor of treatment remission.

We observe that complete histological remission to an 8-week PPI trial was associated with a higher probability of sustained histological remission. Therefore, patients with partial initial remission should be monitored closely for histological recurrence. The underlying mechanisms of PPI responsiveness in EoE may involve anti-inflammatory properties such as the inhibition of T-helper 2 cytokine-induced eotaxin-3 expression in esophageal epithelial cells (25,26). Restoration of esophageal mucosal integrity with high-dose PPI (40 mg dose/twice a day) has been observed (27). Although mislabelling of the initial biopsy sampling cannot be excluded in patients with initial partial remission, it could be speculated that, in some patients, higher doses of PPI might be needed to achieve anti-inflammatory or mucosal restoration mechanisms.

Notably, we included 4 children with EoE under food OIT who presented initial and long-term remission to PPI without food discontinuation. An association between EoE and OIT has been observed in 2.7% to 6.25% of patients after OIT for milk, egg, and peanuts (28,29). Clinical-histological remission can be achieved after food OIT discontinuation (28), but this could be risky for some patients with severe anaphylactic reactions in case of transgressions. Therefore, long-term PPI treatment could be an alternative in children undergoing OIT.

In our study, adverse effects in children under PPI treatment were infrequent and mild; appeared during induction treatment with higher doses and resolved spontaneously or by switching to another PPI agent, without treatment discontinuation. We did not observe esophageal candidiasis as reported in adults (10). In recent years, growing concerns about complications of long-term PPI treatment have emerged, but the general long-term safety of these medications in adults is very good (11,30,31). No major safety concerns arose during 5 to 12 years of continuous PPI therapy in adults in the SOPRAN and the LOTUS study (comparing long-term omeprazole with anti-reflux surgery) (32). Data on the safety of long-term PPI treatment in children are scarce; some studies indicate a potential increased risk of respiratory tract or gastrointestinal infections (12,33). Due to the potential adverse events of long-term PPI treatment, the lowest effective dose should be used to minimize the risk.

The main strength of this study is the prospective design with a uniform protocol for treatment induction, maintenance treatment, and follow-up schedule in both centres. Nevertheless, the study has some potential shortcomings. Adherence to PPI treatment was not specifically assessed by questionnaire and/or recovery of empty medication containers, although it was asked at regular follow-up visits. Clinical outcome was not assessed by a validated questionnaire but was evaluated by means of global remission. As stated before, symptoms are not a good indicator for predicting histological remission (20,21). The CYP2C19 genotype, which has shown to predict long-term response to tapering PPI doses, was not evaluated (9). In addition, in children with loss of response, we did not assess histological response after PPI dose intensification, which was shown to effectively rescue up to 70% of patients who lost response over time (9). We considered that these doses ($1\,mg \cdot kg^{-1} \cdot dose^{-1}$ twice a day) may be too high to maintain long-term because of possible adverse effects.

In conclusion, our findings indicate that 70% of children with PPI-responsive EoE maintain histological remission with long-term treatment at half of the induction dose. Patients with complete initial histological remission have a higher probability of long-term histological remission. Adverse effects were infrequent, mild, and transient.

Further comparative studies should address, which patients may benefit from long-term treatment, the optimal PPI dose, and treatment duration.

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