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Proton pump inhibitor therapy reverses endoscopic features of fibrosis in eosinophilic esophagitis

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ABSTRACT

Background: Long-standing inflammation leads to esophageal remodeling with stricture formation in patients with eosinophilic esophagitis (EoE). The ability of proton pump inhibitors (PPI) to reverse endoscopic features of fibrosis is still unknown.

Objective: To investigate the effect of a short course of PPI treatment in reducing endoscopic findings indicative of esophageal fibrosis in EoE patients.

Methods: Cross-sectional analysis of the EoE CONNECT registry. Patients who received PPI to induce EoE remission were evaluated. Endoscopic features were graded using the EoE Endoscopic Reference Score (EREFS), with rings and strictures indicating fibrosis. Results were compared to those from patients treated with swallowed topic corticosteroids (STC).

Results: Clinico-histological remission was achieved in 83/166 adult patients treated with PPI (50%) and in 65/79 (82%) treated with STC; among responders, 60 (36%) and 57 (72%) patients respectively achieved deep histological remission (<5 eosinophils/hpf). At baseline, mean±SD EREFS was lower in patients treated with PPI compared to those who received STC ($p < 0.001$). Short term treatment significantly reduced EREFS scores in patients treated either with PPI or STC as well as rings and strictures. Among patients treated with PPI, deep histological remission (<5 eosinophils/hpf) provided further reduction in total EREFS score.

Conclusion: Effective PPI therapy for EoE significantly reduced endoscopic esophageal fibrosis in the short term.

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease that is characterized by esophageal dysfunction and transmural infiltration of the esophagus by eosinophils [1,2]. The diagnosis of EoE is reached after performing an endoscopy with biopsies from patients with a range of signs and symptoms, the most common being dysphagia and food impaction. In the majority of cases, the natural course of EoE is chronic and appears to be progressive, with long-standing eosinophilic inflammation leading to esophageal remodeling with stricture formation and functional damage in the long term [3,4]. Therefore, significant morbidity may be associated with EoE, with esophageal strictures requiring repeated mechanical dilations [5].

EoE alters the endoscopic appearance of the esophagus; the reporting of major endoscopic features of this disease has been standardized in the Endoscopic Reference Score classification system (or EREFS), which includes Edema, Rings, Exudates, Furrows and Strictures [6]. This validated system may help to identify inflammatory (i.e. edema, exudates and furrows) versus fibrotic features (i.e. rings and strictures) in the esophagi of EoE patients [7,8]. A moderate-to-good inter-observer and intra-observer agreement has been demonstrated for EREFS [9,10] and, when used prospectively, the EREFS system identifies esophageal abnormalities in more than 95% of patients with EoE [11,12].

First-line anti-inflammatory treatment options for EoE include dietary therapy, swallowed topic corticosteroids (STC) and proton pump inhibitors (PPIs). As EoE represents a particular form of food allergy, diet remains the only therapy targeting the cause of the disease [13]. However, the high levels of restriction some modalities impose and the dependence on repeated endoscopies to identify food triggers are deterrents for its generalization in clinical practice. STC, including budesonide or fluticasone, improve symptoms and inflammation in patients with EoE, as confirmed in multiple trials [14]; specific formulations designed to coat the esophageal surface induce and maintain high rates of histological remission in the long-term [15]. Both dietary therapy and STC have been shown to improve histological [16,17] and endoscopic [15,18,19] features and reverse fibrous remodeling in patients with EoE, which is accompanied by an increase in esophageal distensibility [20]. However, PPIs are the most commonly prescribed first-line therapy for EoE [21–23] because of their low cost, safety profile and convenience, despite inducing remission in only half of the patients [24]. At present, there is no evidence of the potential effect of PPIs in reversing fibrosis in EoE. However, a limited impact of PPIs on subepithelial phenomena such as fibrosis is suggested, since they do not inhibit Th2 cytokine-stimulated eotaxin-3 expression by esophageal fibroblasts *in vitro* [25].

In this study we investigate the potential effect of short-term PPI therapy in reducing endoscopic findings and in reverting EoE fibrotic features, and compare this with STC use, the best documented EoE treatment option.

2. Patients and methods

2.1. Study design and data collection

A cross-sectional analysis of the "European Registry of Clinical, Environmental and Genetic Determinants in Eosinophilic Oesophagitis" (EoE CONNECT) was performed to compare the effectiveness of PPIs and STC in reducing endoscopic features of fibrosis. EoE CONNECT is an international, multicenter, non-interventional registry promoted by United European Gastroenterology in 2016 as part of the Link Award program. Prospective clinical and demographic data from EoE patients of all ages was imputed onto the registry by practitioners during face-to-face clinical appointments. Adult patients who were treated with PPIs or STC in mono-therapy to induce disease remission were selected for this study.

Before and after a short course of treatment (usually 8 to 12 weeks), participants underwent an upper endoscopy, during which at least 6 esophageal biopsies from the distal, middle and/or the proximal esophagus were taken, focused on the most visible endoscopic findings. Esophageal eosinophil counts per high-power field (hpf) in all samples obtained was assessed. Endoscopic appearance of the esophagus was graded by the presence and severity of edema (decreased vascular markings), rings, exudates, furrows, and stricture(s) in accordance with the EREFS grading and classification system [6]. Total EREFS (0-9) was calculated by summing the severity scores of the 5 individual major components (edema 0-1, rings 0-3, exudates 0-2, furrows 0-1 and strictures 0-1), and the minor finding of crepe paper esophagus (mucosal fragility or laceration upon passage of endoscope, 0-1), with higher scores indicating more severe endoscopic findings: Rings and strictures were classified as fibrotic features while edema, furrows and exudates were defined as inflammatory ones [5].

To provide further evidence on the effects for PPI and STC over esophageal fibrous remodeling, changes in esophageal distensibility were measured by functional luminal imaging probe (EndoFLIP; Crospon Medical Devices, Galway, Ireland) in a subset of patients who responded to PPI and STC. At the end of the endoscopy, the EndoFLIP was placed transorally until the bag was positioned through the esophagogastric junction (EGJ). Stepwise distension starting with a bag volume of 20 mL up to maximum to 60 mL was performed at 20 s intervals. After completing the EGJ measures, the EndoFLIP bag was deflated and repositioned into the esophageal body to provide a measurement of the esophageal body and the stepwise distention was repeated. The EndoFLIP bag was subsequently deflated and removed to complete the endoscopy biopsy protocol. Results were analyzed as proposed by Pandolfino el al [26].

Patients who underwent esophageal dilation and those who received therapy combined with other drugs or diets able to reduce eosinophilic inflammation were not considered for this study. Data quality and completion of EoE CONNECT was monitored as previously described [24]. The study protocol conforms to the ethical guidelines of the 1975 Helsinki Declaration of the World Medical Association on principles for medical research involving human subjects. The Clinical Research Ethics Committee at the University Hospital *La Princesa* approved the EoE COMNNECT registry on October, 5th 2015 acting as the central committee. In addition, Ethics Committees in all participating centers confirmed this approval for each site. All patients registered or their legal guardians provided written informed consent.

2.2. Definitions

Active principle, daily dose and dose regime used were recorded. Standard doses of PPI included omeprazole 20 mg, pantoprazole 40 mg, 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 gastroesophageal reflux disease (http://www.whocc.no/atc_ddd_index/?code1/C&showdescription1/4yes, accessed April 4, 2020), consensus guidelines and experimental research [27,28]. Double doses or higher of the above were considered high-dose PPI, and a low dose was defined when PPIs were given under standard doses.

Active EoE was defined as a peak eosinophilic infiltrate by ≥15 eosinophils per high power field (eos/hpf) at any esophageal level together with ≥5 points in the Dysphagia Symptoms Score (DSS) as provided by adult patients. The DDS is a non-validated instrument

developed by Straumann et al [29] repeatedly used to measure EoE symptoms [21,30–32].

Peak eosinophil counts <15 eos/hpf at all levels were considered histological remission; <5 eos/hpf was defined as deep esophageal remission. A decrease of more than 50% in baseline DDS after PPI therapy was considered clinical remission, as previously defined; [21,24,31,32] a symptomatic improvement ≤50% from baseline was considered as a clinical 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 eos/hpf) after therapy. Having <5 eos/hpf and clinical remission after PPI or STC therapy was defined as deep clinico-histological remission. Continuation or worsening of symptoms with persistence of histological activity was considered lack of efficacy.

2.3. Statistical analysis

Numerical data are presented as either mean ± standard deviation (SD) (normally distributed data) median, interquartile range (IQR), or range (nonparametric data). Proportions were used 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 analyzed by chi-square or t-student test (and Fisher exact test when it was appropriate). Differences in EREFS overall score and subscores were compared between EoE responders and non-responders to PPI or STC treatments by chi-square and t-test analyses; changes in EREFS induced by therapy from baseline were compared by McNemar test and paired t-test. All analyses were carried out using PASW 18.0 statistical analysis software (SPSS Inc, Chicago, Ill, USA). A p value < 0.05 was considered significant.

3. Results

3.1. Study population

A search carried out in EoE CONNECT in June 2020 identified 166 and 79 adult patients with active EoE who were treated exclusively with PPIs and STC respectively to induce disease remission, and had information registered before and after therapy on clinical, histological and endoscopic features evaluated, the latter graded according to ERFES system. **Table 1** summarizes the main demographic and clinical characteristics of EoE patients analyzed for this study. Age (mean ± SD) at diagnosis for the overall series was 36.0 ± 16.0 and 190 were male. Duration of therapy was not significantly different between PPI and STC. Patients treated with STC presented a greater EREFS score (mean ± SD) at baseline compared to those who received PPIs (3.77 ± 1.97 vs. 2.65 ± 1.74, p<0.001) as more patients treated with STC had a stricturing EoE: strictures were described at baseline endoscopy in 33 patients treated with STC (42%) but in only 22 patients (13%) treated with PPI. In contrast, a similar prevalence of esophageal rings was found in both patients treated with PPIs and STC (57% and 51%, respectively). A description of the drugs and doses used to induce remission of EoE is shown in **Table S1**.

3.2. Effectiveness of therapy to induce clinico-histological remission of EoE

PPIs led to clinico- histological remission (<15 eos/hpf) in 83 (50%) of the patients treated overall. By comparison, 65 patients (82%) achieved peak eosinophil counts <15 eos/hpf after STC therapy. Of these, deep clinico-histological remission (<5 eos/hpf) was achieved in 60 patients (36%) treated with PPIs and in 57 patients (72%) who received STC (**Table 1**).

3.3. Effect of therapy on endoscopic finding and fibrotic features

At baseline, endoscopic features of fibrosis (i.e., rings and/or strictures) were present in 99 of the patients treated with PPI (60%) and in 50 of those treated with STC (63%). Overall, EoE therapy led to significant reductions in mean ± SD EREFS total scores from baseline in the whole series of PPI (2.65 ± 1.74 vs. 1.61 ± 1.64; p<0.001) and STC-treated patients (3.77 ± 1.97 vs. 0.73 ± 1.45; p<0.001) (**Table 1**).

Among patients who achieved clinico-histological remission of EoE, the EREFS total score was reduced from baseline in both patients treated with PPI (from 2.54 ± 1.79 to 1.01 ± 1.01; p<0.001) and with STC (from 3.74 ± 2.00 to 0.69 ± 1.48; p<0.001). With regard to fibrotic endoscopic features, EREFS subscores for rings (0.81 ± 0.85 vs. 0.45 ± 0.63; p<0.001) and strictures (0.10 ± 0.30 vs. 0.01 ± 0.11; p=0.007) were reduced from baseline in response to PPI therapy; and similarly in patients who responded to STC (0.82 ± 0.99 vs. 0.34 ± 0.73; p<0.001, and 0.42 ± 0.50 vs. 0.03 ± 0.17; p<0.001, EREFS subscores respectively for rings and strictures) (**Table 2**). The absolute changes in EREFS total score and subscores from baseline are shown in **Fig. 1.**

No differences were observed in the baseline endoscopic characteristics of the patients who did and did not respond to treatment with PPI or STC, thus preventing identification of endoscopic features predictive of response (**Table 3**).

3.4. Effect of deep histological remission on reversion of fibrotic endoscopic features

Deep histological remission (<5 eos/hpf) led to additional significant reductions in the EREFS total score (mean ± SD) over those of patients who achieve 5 to 14 eos/hpf after PPI therapy (0.88±0.89 vs. 1.35±1.23, respectively, p=0.044) at the expense of a reduction in inflammatory findings (i.e., furrows), but not in fibrotic features: Rings frequency among patients who achieved partial compared to deep remission after PPI therapy was higher at baseline (43% vs. 35%, respectively), but no statistically significant differences were found. The same was observed among patients treated with STC (38% vs. 18%). A trend towards an additional reduction in the EREFS total score among patients who achieved deep histological remission after STC was also observed (0.60±1.45 vs. 1.38±1.60; p=0.16) (**Table S2**).

3.5. Changes in esophageal distensibility induced by therapy

EndoFLIP assessment was performed in 7 and 6 adult EoE patients who responded to PPI and STC, respectively. At baseline conditions, the slope of the narrowest esophageal diameter-bag volume curve was reducer for patients undergoing treatment wth STC, indicating a lower esophageal compliance compared to patients undergoing PPIs. Treatment with both PPIs and STC increased significantly median narrowest esophageal diameters for all stepwise bag volume increases compared to baseline; differences in esophageal diameter achieved statistical significance for 50 mL volume after PPI effective therapy, and for all diameters over 40 mL among responders to STC. Diameter-volume curves are shown in **Fig. 2**. Demographic and clinical characteristics of patients assessed with endoFLIP are shown in **Table S3.**

4. Discussion

This study constitutes, to the best of our knowledge, the first demonstration of the ability of PPI therapy to reverse the fibrotic

Table 1
Demographic and clinical characteristics of patients with eosinophilic esophagitis (EoE) treated with proton pump inhibitors (PPI) or swallowed topic corticosteroids (STC) and endoscopic assessment registered in the EoE CONNECT database.

	PPI treated EoE patients (*n*=166)	STC treated EoE patients (*n*=79)	*p* value*
Age at diagnosis, years (mean±SD)	37.1 (27–46)	34.8 (26–45)	0.56
Male (*n*, %)	124 (75)	66 (83)	0.12
Treatment length up to evaluation, days (median, IQR)	71 (62–105)	58.5 (45–122)	0.16
EoE phenotype (*n*, %) #			
Inflammatory	140 (86)	44 (58)	<0.001
Mixed	14 (9)	11 (14)	
Stricturing	9 (5)	21 (28)	
Baseline EREFS score (mean±SD)	2.65 ± 1.74	3.77 ± 1.97	<0.001
Post treatment EREFS score (mean±SD)	1.61 ± 1.64	0.73 ± 1.45	<0.001
Clinico-histological remission (<15 eos/hpf) (*n*,%)	83 (50)	65 (82)	<0.001
Deep clinico-histological remission (<5 eos/hpf) (*n*, %)	60 (36)	57 (72)	<0.001
Partial clinico-histological remission (5–14 eos/hpf) (*n*, %)	23 (14)	8 (10)	0.10
Endoscopic features of fibrosis, patients (*n*, %)	99 (60)	50 (63)	0.21
Rings, patients (*n*, %)	94 (57)	40 (51)	0.19
Stricture, patients (*n*, %)	22 (13)	33 (42)	<0.001

*Proportions are compared with chi-square; means are compared with two sample t-test. #As classified by endoscopists according to predominant endoscopic features

Table 2
Changes in EREFS total score and subscores for each EREFS component induced by effective treatment with proton pump inhibitors (PPI) and swallowed topic corticosteroids (STC) in patients who achieved clinico-histological remission of eosinophilic esophagitis.

EREFS (inflammatory features)	PPI responder patients (*n*=83)			STC responder patients (*n*=65)		
	Baseline	After treatment	*p* value*	Baseline	After treatment	*p* value*
Edema (*n*, %)						
0	48 (58)	71 (87)	**<0.001**	22 (34)	59 (91)	**<0.001**
1	34 (42)	11 (13)		43 (66)	6 (9)	
Subscore (mean±SD)	0.41±0.50	0.13±0.34	**<0.001**	0.66±0.48	0.09±0.29	**<0.001**
Furrows (*n*, %)						
0	31 (37)	57 (69)	**<0.001**	19 (29)	58 (89)	**<0.001**
1	52 (63)	26 (31)		46 (71)	7 (11)	
Subscore (mean±SD)	0.63±0.49	0.31±0.47	**<0.001**	0.71±0.46	0.11±0.31	**<0.001**
Exudates (*n*, %)						
0	47 (57)	76 (92)	**<0.001**	25 (39)	60 (92)	**<0.001**
1	29 (35)	7 (8)		23 (35)	4 (6)	
2	7 (8)	0		17 (26)	1 (2)	
Subscore (mean±SD)	0.52±0.65	0.08±0.28	**<0.001**	0.88±0.80	0.09±0.33	**<0.001**
EREFS (fibrotic features)						
Rings (*n*, %)						
0	36 (43)	52 (63)	**0.012**	35 (54)	52 (80)	**0.005**
1	30 (36)	25 (30)		11 (17)	5 (8)	
2	14 (17)	6 (7)		15 (23)	7 (11)	
3	3 (4)	0 (0)		4 (6)	1 (1)	
Subscore (mean±SD)	0.81±0.85	0.45±0.63	**<0.001**	0.82±0.99	0.34±0.73	**<0.001**
Strictures (*n*, %)						
0	75 (90)	82 (99)	**0.016**	38 (58)	63 (97)	**<0.001**
1	8 (10)	1 (1)		27 (42)	2 (3)	
Subscore (mean±SD)	0.10±0.30	0.01±0.11	**0.007**	0.42±0.50	0.03±0.17	**<0.001**
EREFS (minor features)						
Crepe paper esophagus (*n*, %)						
0	75 (90)	82 (99)	**0.039**	48 (74)	63 (97)	**<0.001**
1	8 (10)	1 (1)		17 (26)	2 (3)	
Subscore (mean±SD)	0.10±0.30	0.01±0.11	**0.019**	0.26±0.44	0.03±0.17	**<0.001**
Total EREFS score (mean±SD)	2.54±1.79	1.01±1.01	**<0.001**	3.74±2.00	0.69±1.48	**<0.001**

*For comparison of STC or PPI-responsiveness at baseline and post-treatment, McNemar and paired t-tests are used.

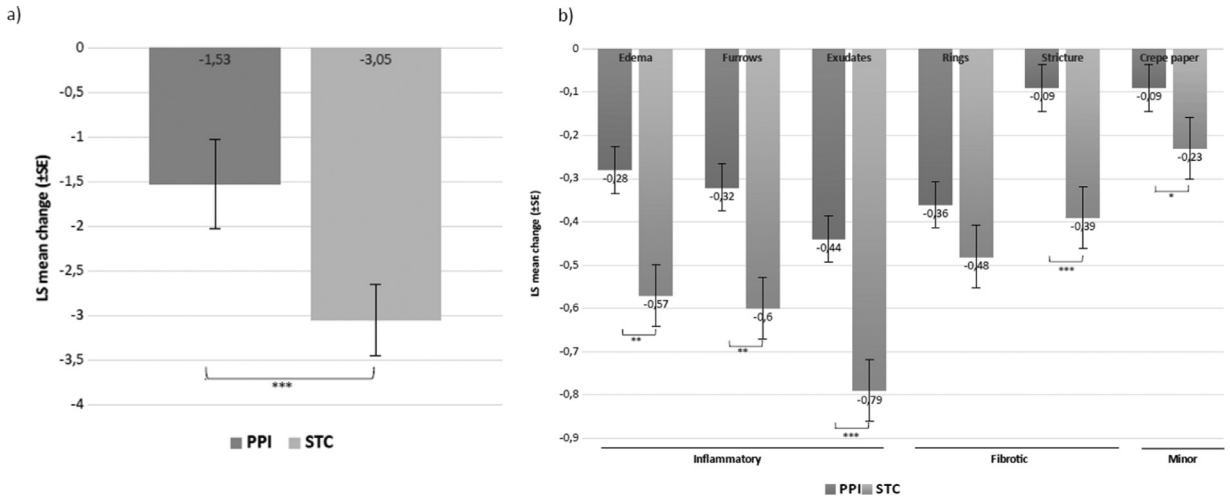

Fig. 1. Absolute changes from baseline in EREFS total score (a) and component subscores (b) in adult patients with eosinophilic esophagitis treated with proton pump inhibitors (PPI) or swallowed topic corticosteroids (STC). LS mean: Least Squares means; $^{*}p < 0{,}05$ $^{**}p < 0{,}01$ $^{***}p < 0{,}001$.

Table 3
EREFS total score and subscores for its components at baseline in patients who did and did not achieved clinico-histological remission of eosinophilic esophagitis after short-term treatment with proton pump inhibitors (PPI) or swallowed topic corticosteroids (STC)

	Patients treated with PPI (n=166)			Patients treated with STC (n=79)		
	Responders (n=83)	Non-responders (n=83)	p value*	Responders (n=64)	Non-responders(n=15)	p value*
EREFS (inflammatory features)						
Edema (n, %)						
0	48 (58)	54 (65)	0.39	22 (34)	4 (31)	0.83
1	34 (42)	29 (35)		43 (66)	9 (69)	
Subscore (mean±SD)	0.41±0.50	0.35±0.48	0.39	0.66±0.48	0.69±0.48	0.83
Furrows (n, %)						
0	31 (37)	33 (40)	0.75	19 (29)	4 (31)	0.91
1	52 (63)	50 (60)		46 (71)	9 (69)	
Subscore (mean±SD)	0.63±0.49	0.60±0.49	0.75	0.71±0.46	0.69±0.48	0.91
Exudates (n, %)						
0	47 (57)	42 (50)	0.35	25 (39)	5 (38)	0.97
1	29 (35)	28 (34)		23 (35)	5 (38)	
2	7 (8)	13 (16)		17 (26)	3 (24)	
Subscore (mean±SD)	0.52±0.65	0.65±0.74	0.22	0.88±0.80	0.85±0.80	0.90
EREFS (fibrotic features)						
Rings (n, %)						
0	36 (43)	36 (43)	0.93	35 (54)	3 (23)	0.06
1	30 (36)	27 (33)		11 (17)	6 (46)	
2	14 (17)	16 (19)		15 (23)	4 (31)	
3	3 (4)	4 (5)		4 (6)	0	
Subscore (mean±SD)	0.81±0.85	0.86±0.90	0.72	0.82±0.99	1.08±0.76	0.29
Strictures (n, %)						
0	75 (90)	69 (83)	0.17	38 (59)	7 (54)	0.76
1	8 (10)	14 (17)		27 (41)	6 (46)	
Subscore (mean±SD)	0.10±0.30	0.17±0.38	0.17	0.42±0.49	0.46±0.52	0.76
EREFS (minor features)						
Crepe paper esophagus (n, %)						
0	75 (90)	69 (83)	0.17	48 (74)	9 (69)	0.48
1	8 (10)	14 (17)		17 (26)	4 (31)	
Subscore (mean±SD)	0.10±0.30	0.17±0.38	0.17	0.26±0.44	0.31±0.48	0.74
Total EREFS score (mean±SD)	2.76±1.70	2.54±1.79	0.42	3.74±2.03	4.00±1.78	0.77

*Proportions are compared with chi-square; means are compared with a two sample t-test.

changes associated with EoE by reducing the total EREFS score at endoscopy and, in particular, those features indicating fibrosis after a short course or treatment to induce EoE remission.

Our results add to the available evidence on the effectiveness of STC and dietary therapy in reversing endoscopic features of fibrosis, and to the recently reported evidence for novel biological drugs against the interleukin (IL) 4 receptor, also shown to improve fibrous remodeling at both endoscopic and functional levels [12].

The strengths of our study include the use of a large, multicenter registry of adult patients with EoE, prospectively recruited from several sites within two European countries. The active monitoring of EoE CONNECT ensures the reliability of the registered information. Inclusion criteria required all patients to be fully evaluated for EoE activity at baseline and after PPI or STC-based therapies in terms of symptoms, endoscopy and histology. No patient underwent esophageal dilation, therefore changes in the ERFES score were exclusively attributed to the anti-inflammatory properties of drug therapy.

Some limitations should also be acknowledged however. These include the variability in the use of drugs and dose regimes, according to the criteria of treating physicians, the use of DSS as a non-validated tool to assess dysphagia in all patients, and the ab-

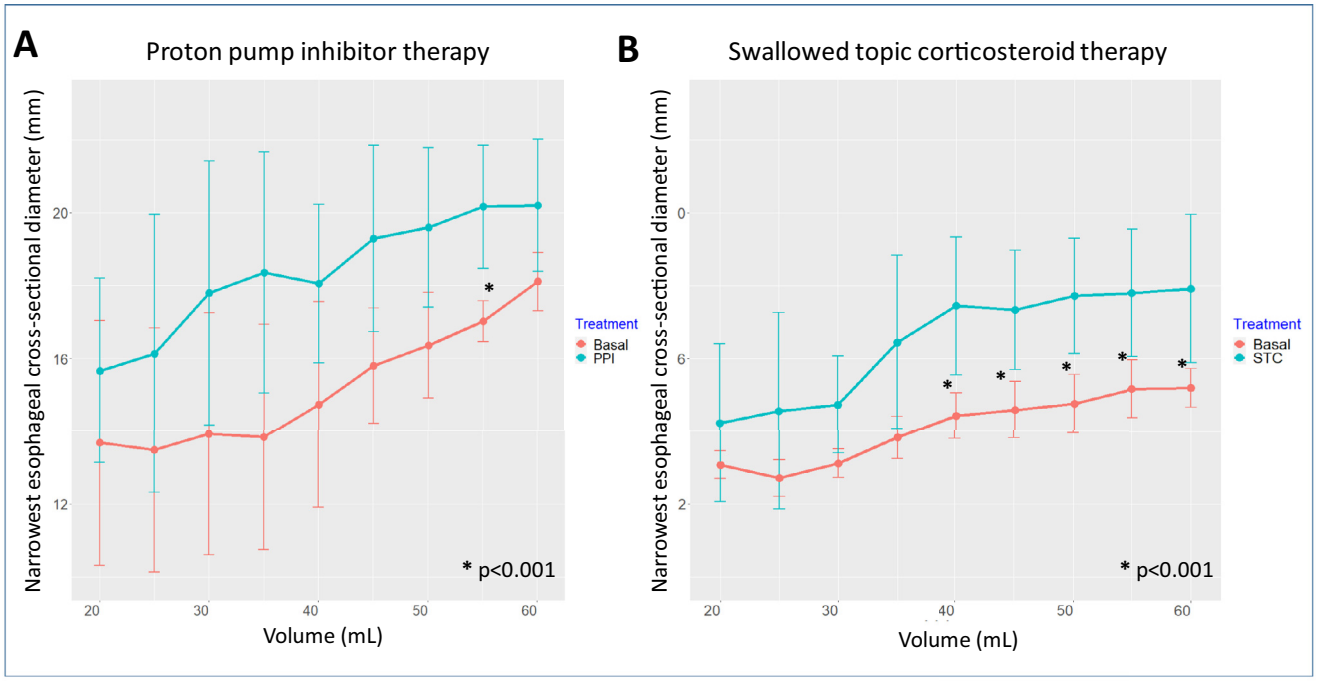

Fig. 2. Esophageal distensibility in adult patients with EoE at baseline (red) and after treatment (blue) with proton pump inhibitors (A) or swallowed topic corticosteroids (B). Dots and whiskers represent median±IQR vales for a subset of 7 and 6 responding EoE patients to PPI and STC therapy, respectively. Esophageal compliance curves were significantly different ($p < 0.001$) at a distension volume of 50 mL for proton pump inhibitors therapy and 40 mL and above for swallowed topic steroids. Data shown as medians with IQR.

sence of central reading of endoscopic images in order to guarantee reliability of EREFS scores provided by recruiters at every site. However, the DSS is widely used to assess symptoms in patients with EoE and has been shown to capture changes induced by therapy [21,31,32] even in randomized placebo-controlled trials [12,29,30]. EndoFLIP was used to objectively assess therapy-induced changes in esophageal diameter in only a small subset of responding patients. Contributors to EoE CONNECT mostly included experts in EoE who routinely use EREFS to describe findings from endoscopic exams. We did not considered children for this study, therefore caution should be used when applying the results to the pediatric population.

In recent years, therapeutic goals for EoE have evolved from the mere control of symptoms and esophageal inflammation, to recovering the caliber of this organ and reversing its structural damage, restoring its functionality and improving patients' health-related quality of life (HRQoL). The most recent trials aimed at developing new drugs for EoE now include, as relevant study outcomes, normalization of endoscopic appearance of the esophagus and that of esophageal distensibility, measured using high-resolution impedance planimetry recordings during a volume-controlled distention [32]. Esophageal distensibility parameters in patients with EoE and normal endoscopy have been seen to be similar to those of normal subjects; whereas patients with EoE and stricture or narrow caliber esophagus had much lower distensibility [33–35]. The recognition of EoE as a transmural disease, in which the eosinophilic infiltration permeates deep into the esophageal submucosa, the muscle layers, and the neuronal plexus [2] explains the repeatedly reported disconnection between the severity of mucosal eosinophilia and severity of symptoms [34,36], and provides a basis for attributing phenomena in the layers beneath the submucosa as major determinants for symptoms in EoE. Patients with prior food impactions present significantly lower distensibility plateau values than those with solid food dysphagia alone, and patients who require esophageal dilation during the course of their disease also have significantly lower distensibility than those who do not [34,37]. In addition, fibrotic changes in EoE are major determinants for HRQoL: the severity of endoscopic features [7], including the presence of esophageal strictures at diagnosis leading to recurrent food impaction [38], significantly impair HRQoL in EoE. Disease duration is directly associated with fibrous remodeling and the risk of esophageal strictures [3,4] and is also shown to determine HRQoL in EoE [38,39]. All these findings underline the importance of reversing and avoiding the development of fibrosis in the esophagus, as well as ensuring an adequate esophageal caliber from the early stages of treatment of EoE patients, which goes beyond just the effective control of biological activity of the disease by drug or diet-based anti-inflammatory therapies.

In conclusion, this research provides evidence on the effectiveness of anti-inflammatory therapy with PPIs to reverse features of fibrosis in adult patients with EoE who achieve remission after a short course treatment, and supports PPI as a first line approach to EoE treatment [40]. Deep histological remission provided further benefit in real-world practice, thus supporting the role of PPIs as a first-line treatment option for patients with EoE.

Conflict of interest

None of the authors have any conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.05.025.

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