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Budesonide orodispersible tablets for induction of remission in patients with active eosinophilic oesophagitis: A 6-week open-label trial of the EOS-2 Programme

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Abstract

Background: A novel budesonide orodispersible tablet (BOT) has been proven effective in adult patients with active eosinophilic oesophagitis (EoE) in a 6-week placebo-controlled trial (EOS-1).

Aims: To report the efficacy of an open-label induction treatment with BOT in a large prospective cohort of EoE patients within the EOS-2 study.

Methods: Patients with clinico-histological active EoE were treated with BOT 1 mg BID for 6 weeks. The primary endpoint was clinico-histological remission (≤2 points on numerical rating scales [0–10] each for dysphagia and odynophagia, and peak eosinophil count <16 eos/mm^2 hpf (corresponds to <5 eos/hpf)). Further study endpoints included clinical and histological remission rates, change in the EEsAI-PRO score, change in peak eosinophil counts, and deep endoscopic remission using a modified Endoscopic Reference Score.

Results: Among 181 patients enrolled, 126 (69.6%) achieved clinico-histological remission (histological remission 90.1%, clinical remission 75.1%). The mean peak eosinophil counts decreased by 283 eos/mm^2 hpf (i.e., by 89.0%). Mean EEsAI-PRO score decreased from baseline by 29 points and deep endoscopic remission was achieved in 97 (53.6%) patients. The majority of patients judged tolerability as good or very good (85.6%) and compliance was high (96.5%). Local candidiasis was suspected in 8.3% of patients; all were of mild severity, resolved with treatment and none led to premature withdrawal from the study.

Conclusions: In this large prospective trial, a 6-week open-label treatment with BOT 1 mg BID was highly effective and safe in achieving clinico-histological remission of active EoE and confirmed the results of the placebo-controlled EOS-1 trial.

KEYWORDS
budesonide, dysphagia, eosinophilic oesophagitis, topical corticosteroids

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated, organ-restricted disease, characterized by symptoms of oesophageal dysfunction and an eosinophil-predominant inflammation of the oesophagus.[1] Over the last 2 decades, the incidence and prevalence of EoE have constantly increased, especially in Western countries.[2] EoE is now regarded as the most common cause of dysphagia and bolus impaction[3,4] and the second leading cause of chronic oesophagitis after gastro-oesophageal reflux disease (GORD).[5]

In adult EoE patients, the predominant symptoms are chronic dysphagia, food impaction and chest pain.[1] EoE is a chronic-progressive disease and, if left untreated, is usually associated with persistence of symptoms and inflammation.[6] In addition, ongoing eosinophilic inflammation may lead to oesophageal remodeling resulting in fibrosis with possible stricture formation and functional damage in a large proportion of patients.[7–9] Health-related quality of life (HRQoL) is substantially impaired in EoE patients by causing emotional distress and restricting social activities.[10] Therefore, treatment of active EoE is mandatory.[1,11]

Swallowed topical corticosteroids (STC) are an established first-line pharmacologic treatment option for patients with EoE.[1,11] In the absence of approved formulations for EoE therapy, STCs (mainly fluticasone or budesonide), originally developed for airway administration in patients with asthma or hospital pharmacy made viscous solutions, have been used in several EoE trials which confirmed the efficacy of these compounds in improving both symptoms and inflammation.[12] However, variability regarding patient selection, daily dosages, length of treatment, mode of delivery, and definition of both histological and clinical remission hampers comparative analyses among these studies.

Recently, a novel budesonide orodispersible tablet (BOT) formulation given 1 mg or 2 mg twice daily has demonstrated equally high effectiveness and safety in short-term treatment of adult patients with active EoE in a placebo-controlled phase 2 trial, achieving up to 100% histological remission rates.[13] In a subsequent phase 3 programme, BOTs were investigated in a double-blind, placebo-controlled induction of remission trial (EOS-1).[14] In this trial, 88 adults with active EoE were randomised to BOTs 1 mg twice daily or placebo given for 6 weeks. Among 59 patients exposed to BOTs, the

rate of clinico-histological remission was 58% compared to 0% with placebo. The corresponding figures for histological remission and clinical remission after 6 weeks of treatment were 93% versus 0% and 58% versus 14%, respectively.[14]

Here, we report the results of an open-label induction of remission treatment in a large prospective cohort of adult patients with active EOE, which served as a feeding arm for the further double-blind maintenance treatment (EOS-2) within the phase 3 programme.[15]

Key summary

Summarize the established knowledge on this subject

- The novel budesonide orodispersible tablet (BOT) was effective and safe for induction of clinico-histological remission in 88 adults with active eosinophilic esophagitis (EoE) in a pivotal phase 3 placebo-controlled trial (EOS-1).
- BOT is currently the only drug licensed for treatment of EoE in adults.
- More knowledge on BOT in larger patient cohorts is need.

What are the significant and/or new findings of this study?

- BOT is highly effective for induction of clinico-histological remission in 181 adults with active EoE and confirmed the results observed in the double-blind, but much smaller, pivotal EOS-1 trial.
- Induction therapy with BOT achieves histological remission in 90% of patients.
- During a 6-week course of treatment, BOT was safe and well tolerated.

METHODS

Study design and conduct

The EOS-2 study was a randomized, double-blind, placebo-controlled, multi-centre, 48-week maintenance trial, with an optional 96-week open-label extension, and with a 6-week open-label induction of remission phase (OLI) in adult patients with active EoE, which served as a feeding arm for the maintenance part. The open-label induction and the double-blind part of the study were conducted at 35 centres (see the Supplementary Appendix) in six European countries from January 2016 to November 2018. The study protocol was approved by the national ethics committees in all participating countries and registered at www.clinicaltrialsregister.eu (EudraCT 2014-001485-99) and at www.clinicaltrials.gov (NCT02434029). All patients provided written informed consent. The study was conducted in accordance with the protocol, European Medicines Agency Guidelines for Good Clinical Practice, and within the provisions of the Declaration of Helsinki. The first draft of the manuscript was written by the first author; all authors had access to the study data and reviewed and approved the final manuscript.

Patients

To be eligible for the open-label induction of remission phase, patients with clinico-histological active EoE (age 18–75 years) who were clinico-histological refractory to proton pump inhibitors (at least standard doses, e.g., omeprazole 20 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, lansoprazole 30 mg/day or rabeprazole 20 mg/day for at least 4 weeks)[16] had to have a severity of ≥4 points on a 0–10 numerical rating scale (NRS) for either dysphagia or odynophagia for ≥1 day in the week before baseline. Additionally, patient's global assessment (PatGA) of EoE activity had to be ≥4 points on a 0–10 NRS. As in the previous double-blind induction trial,[14] histological activity with peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf with an hpf area of 0.3072 mm^2), as measured in a total of 6 hpfs derived from six biopsies, two each from the proximal, mid and distal segments of the oesophagus, had to be confirmed. Both, steroid-naïve as well as patients who previously have been treated with topical steroid formulations (e.g., self-made swallowed topical steroid formulation) were allowed to enter the screening phase.

Key exclusion criteria were GORD demonstrated by either pathologic pH-monitoring or erosive oesophagitis (at least Los Angeles Classification Grade A), achalasia or scleroderma; evidence of causes other than EoE for oesophageal eosinophilia; pathological eosinophilic infiltration in gastric and duodenal biopsies; history of oesophageal surgery at any time or of oesophageal dilation procedures within the last 8 weeks prior to screening; esophageal strictures not passable with a standard gastroscope; any relevant systemic disease; systemic corticosteroids, immunosuppressants, biological drugs within 4 weeks prior to screening, or STCs within 2 weeks prior to screening; onset of dietary restrictions within 4 weeks prior to screening.

Therapy

At baseline and at weeks 2 and 4, eligible patients received study medication for the next period. The orodispersible tablet was administered twice daily and was placed on the tip of the tongue and pressed gently against the hard palate until it had completely disintegrated by contact with saliva, whose production was stimulated by the slight effervescence of the study medication.[15] The components dissolved in saliva were then to be swallowed (approximately 10 swallows within several minutes). Patients were instructed to avoid eating, drinking or oral hygiene procedures for 30 min after study drug administration. Compliance was assessed by pill count. The use of other concomitant anti-inflammatory drugs (i.e., systemic or topical corticosteroids, immunosuppressants, biological drugs) or onset and change of dietary restrictions was not permitted.

Procedures

Visits took place every 2 weeks during the 6-week open-label treatment, followed by a 4-week follow-up visit, if the patient did not switch to the EOS-2 double-blind maintenance of remission phase.[17] Clinical symptoms were assessed during the 7 days prior to baseline, and throughout the study using 0–10 point NRSs with obvious face validity for dysphagia and odynophagia, respectively. At all visits, patients completed the PatGA of EoE activity (0–10 NRS) and the validated Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score (0–100 points).[18] Physician's global assessment (PGA) of EoE activity (0–10 NRS) was assessed at baseline and week 6. Patients completed the EoE-QoL-A questionnaire v.2.0[19] (licensed from Northwestern University) and a modified Short Health Scale (SHS)— a visual analogue scales questionnaire (range 0–100 with lower values indicating better quality of life, questions representing each of four health dimensions: (1) symptom burden, (2) social function, (3) disease-related worry, and (4) general well-being). Upper endoscopy was performed during screening and at week 6. The most severe findings from the total oesophagus were classified according to the modified Endoscopic Reference Score (EREFS) grading system.[20] In addition, a global assessment of endoscopic EoE activity was performed and classified as 'none', 'mild', 'moderate' or 'severe'.

At each endoscopy, two biopsies each from the distal, mid and proximal oesophagus were obtained and analysed by the central pathologist (M.V.). In addition, biopsies from the stomach and duodenum were obtained at screening, to exclude concomitant diseases such as eosinophilic gastroenteritis. Biopsy specimen were fixed in 4% neutral-buffered formalin and embedded in paraffin. On each 4 μm thick hematoxylin & eosin-stained oesophageal biopsy specimen, all levels were surveyed and the eosinophils in the most densely infiltrated area were counted and reported as eos/mm^2 hpf. For standardization within the study, as well as between the previous studies (BUU2, BUL1, BUL2) and since we based our sample size calculation in our EoE programme on the histological remission rates reported by Straumann et al.,[21] we back-calculated the cut-off value of <5 eos/hpf for histological remission based on the reported microscopic field of 0.3072 mm^2 in the study by Straumann et al.,[21] which corresponds to <16 eos/mm^2 hpf. In patients with suspected local fungal infection (i.e., based either on clinical symptoms, endoscopic appearance or from suspicious HE-stained histological slides), sensitive Grocott silver staining was performed for final confirmation, followed by antifungal treatment, if needed.

Safety and tolerability

Physical examinations were performed during screening and at week 6. Vital signs, concomitant medications and adverse events were recorded, and general laboratory tests and urinalysis were performed. Serum morning cortisol (8–9 AM) levels were measured at baseline and week 6. Tolerability was classified independently by the patient and the investigator at week 6.

Study endpoints

The primary efficacy endpoint for the open-label induction phase was the rate of patients with clinico-histological remission at week 6, that is, achieving *both* histological remission (peak eosinophil count <16 eos/mm^2 hpf [corresponds to <5 eos/hpf as reported by Straumann et al.[21]]) and clinical remission (symptoms severity of ≤2 points on each 0–10 NRS for dysphagia and odynophagia, respectively, on each day in the week prior to week 6). Occurrence of food impaction, need for endoscopic intervention or dilation, or premature withdrawal was assessed as treatment failure. Secondary endpoints included histological and deep histological remission (i.e., 0 eos/hpf), absolute and relative change in peak eosinophil counts, resolution of symptoms on each day in the week prior to each visit, course of clinical remission defined as EEsAI-PRO ≤20, deep clinical remission (NRS 0 for dysphagia and odynophagia), deep endoscopic remission (modified EREFS subscores: fixed rings = '0' or '1', exudates = '0', furrows = '0' and oedema = '0'),[22,23] deep disease remission (deep clinical remission + deep histological remission + deep endoscopic remission), and HRQL assesed by EoE-QoL-A and modified SHS.

Statistical analyses

Descriptive statistics were used to summarize data, including incidences of adverse events. Analyses were performed using SAS® version 9.3 (SAS Institute Inc.) according to the intention-to-treat principle. Missing data at week 6 were replaced using the last-observation-carried-forward (LOCF) method. Adverse events were classified by using the *Medical Dictionary for Regulatory Activities*,[24] version 19.

RESULTS

Patient enrolment and baseline characteristics

As this open-label arm was used as a second feeding arm for the double-blind maintenance phase of the trial, which was primarily fed by patients rolling over from the EOS-1 trial after having brought into clinico-histological remission, screening was continued until a total of 204 patients were randomized into the double-blind maintenance phase. One hundred eighty-one out of 231 screened patients met the inclusion criteria and were enrolled. Six patients discontinued treatment prematurely and 175 patients completed the open-label treatment phase (96.7%). All 181 patients were evaluable for the primary analysis.

The demography and medical history of the study cohort were typical for an adult patient population with active EoE with respect to age, gender and history of allergic diseases (Table 1). The majority of patients had an established diagnosis of EoE and a long history of disease-related symptoms including bolus obstructions in most cases. Less than half of the patients had a previous exposure to topical corticosteroids. Oesophageal symptom scores at baseline were moderate to severe as assessed by NRS for dysphagia and odynophagia, NRS for PatGA and PGA, and EEsAI-PRO (Table 1). The majority of patients had moderate to severe endoscopic activity based on the endoscopist's assessment and EREFS. Histological activity based on eosinophil counts per mm^2 hpf was evident in all three segments of the oesophagus in the vast majority of patients with a slight gradient from distal to proximal (Table 1).

Clinical efficacy

Clinico-histological remission, as defined as primary endpoint in the double-blind phase of the EOS-1, at week 6 was achieved in 126 patients (69.6%; Figure 1). Thereby, similar results were observed in topical steroid-naïve patients (70 out of 104 patients [67.3%]) as well as in previously topical steroid-exposed patients (56 out of 77 patients [72.7%]). Assessed as single endpoints, clinical remission was achieved in 75.1% and histological remission was achieved in 90.1% of patients (Figure 1), while deep histological remission ('0' eos/hpf) was observed in 84.5% of patients (Figure 2). Histological remission as well as deep histological remission was independently achieved in all oesophageal segments in the range of 89%–94% (Table 2 and Figure 2), indicating that BOT provides an optimal oesophageal targeting. Moreover, the peak eosinophil count was dramatically decreased by 89.0% from baseline confirming that BOT 1 mg BID was able to induce remission even in severely inflamed cases (see Figure 3), where patients with baseline peak eosinophilic counts of even more than '1.000' eos/mm^2 hpf achieved deep histological remission with '0' eos/hpf after 6-week BOT 1 mg BID treatment.

Based on the PatGA, 84.5% of patients reported a drop from ≥4 points prior treatment to ≤2 points at week 6 (LOCF) on the NRS related to the overall assessment of their EoE severity (Figure 4a), with an absolute mean (SD) change of −4 (2.1) points. This was in line with the analogue assessment on EoE by the physician showing an absolute mean (SD) change of −5 (2.2) points from baseline to week 6 (LOCF) as well as with the course of clinical remission defined by symptom resolution (NRS ≤2 for both dysphagia and odynophagia, or by EEsAI-PRO ≤20, respectively (Figure 4b,c), which all showed the quick clinical response to BOT 1 mg BID. Clinical remission, defined as a score of EEsAI-PRO ≤20, was observed in 49.2% of patients (Table 2), with a significant absolute mean (SD) change of −29 (21.4) points.

The modified EREFS total score significantly decreased from baseline to week 6 by −3 points, which was mainly driven by the inflammatory subscore (Table 2). Deep endoscopic remission was achieved in 53.6% of patients, which was in line with the endoscopist's overall global assessment of „no endoscopic signs of EoE' (55.8%; Table 2).

HRQoL as measured by modified SHS and EoE-QoL-A scores was moderately impaired at baseline (Table 3). HRQoL improved significantly from baseline to week 6 (LOCF) based upon the disease specific EoE-QoL-A questionnaire and all its subscores. This was in line with the generic modSHS instrument showing significant improvement in mean scores from baseline to week 6 for all four dimensions.

Safety and tolerability

Overall, BOT 1 mg BID was well tolerated in this study. A total of 60 patients (33.1%) experienced 95 adverse drug reactions (Table 4). Three serious adverse events, all assessed as unrelated to budesonide, were reported for three different patients (1.7%) under treatment: Depression with an onset during pre-treatment, and viral tracheitis as well as a fibula fracture each with an onset during treatment. One SAE (Mallory–Weiss laceration) occurred during screening endoscopy in one patient, who was subsequently not randomized and treated. Clinically manifested suspected local candidiasis assessed to be related to budesonide treatment was reported for 15 patients (8.3%) of which 6 were histologically confirmed (3.3%). All were of mild or moderate intensity, with no impact on daily life activities and recovered after local medical treatment—none of them led to a premature withdrawal from the study. There were no laboratory related treatment-emergent adverse events and no clinically relevant mean (SD) changes from baseline to week 6 (LOCF) in morning serum cortisol levels (baseline: 13.1 [5.39] µg/dl; week 6 [LOCF]: 12.1 [5.57] µg/dl). Decreased blood cortisol, which is a known adverse drug reaction of budesonide, was reported in four patients (2.2%) with possible or probable/likely relationship to the study medication intake. However, in all cases, the severity was mild without any clinical symptoms, no measures were taken and the outcome was recovered/resolved. Five patients (2.8%) prematurely stopped administration of the study medication due to intolerable adverse events, including five AEs that were assessed as probably/likely related to the investigational product (headache, mood altered, hypogeusia, cough and sensation of foreign body). The majority of patients judged tolerability as good or very good (85.6%) and compliance based on pill counts was high (96.5%).

DISCUSSION

This prospective open-label multicentre trial confirmed that a 6-week treatment with BOT 1 mg BID is highly effective and safe for induction of clinical and histological remission in a large adult patient population with active EoE. The composite endpoint used in this study is regarded as the major therapeutic target of any induction therapy of EoE and is therefore recommended by recent European and American guidelines.[1,11] Histological remission is regarded particularly important since chronic eosinophil-predominant

TABLE 1 Demography, medical history and baseline disease characteristics of study patients

Characteristic	BOT 1 mg BID, *N* = 181
Gender, *n* (%)	
Male	146 (80.7)
Age (years), mean (SD)	36.0 (11.5)
Ethnic background, *n* (%)	
Caucasian, *n* (%)	180 (99.4)
Asian, *n* (%)	1 (0.6)
Smoking status, *n* (%)	
Current	13 (7.2)
Former	28 (15.5)
Never	140 (77.3)
Body mass index (kg/m^2), mean (SD)	24.7 (4.1)
EoE history	
New diagnosis, *n* (%)	22 (12.2)
Established diagnosis, *n* (%)	159 (87.8)
Time since EoE diagnosis, years mean (SD)	3.1 (3.0)
Time since first symptoms of disease, years mean (SD)	10.5 (8.9)
Previous or current dysphagia, *n* (%)	174 (96.1)
Previous or current food impaction, *n* (%)	168 (91.7)
Previous dilatations, *n* (%)	18 (9.9)
Family history of EoE, *n* (%)	17 (9.4)
History of allergic diseases, *n* (%)	
Allergic rhinitis	103 (56.9)
Allergic conjunctivitis	66 (36.5)
Allergic asthma	55 (30.4)
Atopic eczema	23 (12.7)
Food allergies	67 (37.0)
Previous corticosteroid exposure, *n* (%)	
Topical corticosteroids	77 (42.5)
Systemic corticosteroids	3 (1.7)
SYMPTOMS	
Dysphagia NRS (0–10), mean (SD); lower values indicate less disease activity	5.7 (1.9)
Odynophagia NRS (0–10), mean (SD); lower values indicate less disease activity	3.8 (2.7)
Number of symptom-free days/week	
Dysphagia NRS (≤2), mean (SD)	1 (2.1)
Odynophagia NRS (≤2), mean (SD)	3 (2.9)
EEsAI-PRO (score 0–100), mean (SD); lower values indicate less disease activity	52 (17)
Patient's global assessment of EoE activity	
(NRS 0–10), mean (SD); lower values indicate less disease activity	6 (1.5)
Physician's global assessment of EoE activity	
(NRS 0–10), mean (SD); lower values indicate less disease activity	6 (1.6)

(Continues)

TABLE 1 (Continued)

Characteristic	BOT 1 mg BID, *N* = 181
Histology	
Number of oesophageal segments affected by inflammation	
1 segment inflamed, *n* (%)	17 (9.4)
2 segments inflamed, *n* (%)	34 (18.8)
3 segments inflamed, *n* (%)	130 (71.8)
Peak number of eosinophils/mm^2 hpf mm^2 hpf	
Total oesophagus, mean (SD)/median [Q25%; Q75%]/N	300 (257)/219 [139; 325]/181
Distal oesophagus, mean (SD)/median [Q25%; Q75%]/N	212 (190)/162 [96; 266]/177
Mid oesophagus, mean (SD)/median [Q25%; Q75%]/N	201 (198)/139 [70; 260]/180
Proximal oesophagus, mean (SD)/median [Q25%; Q75%]/N	174 (229)/116 [46; 225]/180
Endoscopy	
Overall assessment of endoscopic activity, *n* (%)	
None	–(0)
Mild	39 (21.5)
Moderate	100 (55.2)
Severe	42 (23.2)
Modified total EREFS score (0–9), mean (SD), lower values indicate less disease activity	4 (1.6)
Subscore inflammation (0–4), mean (SD); lower values indicate less disease activity	3 (0.9)
Subscore fibrosis (0–4), mean (SD); lower values indicate less disease activity	1 (1.1)

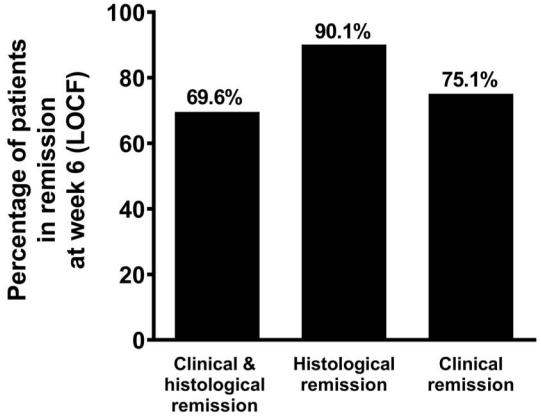

FIGURE 1 Clinical and/or histological remission after 6 weeks of BOT 1 mg BID treatment. Clinical remission: Dysphagia Score ≤2 (NRS 0–10) and Odynophagia Score ≤2 (NRS 0–10) on each day in the last treatment week; Histological remission: <16 eos/mm^2 high power field (hpf) [corresponds to <5 eos/hpf as reported by Straumann et al. 2010] 2010]. BID, twice daily; BOT, budesonide orodispersible tablet; eos, eosinophils; hpf, high power field (400x); NRS, Numerical Rating Scale; LOCF, last observation carried forward

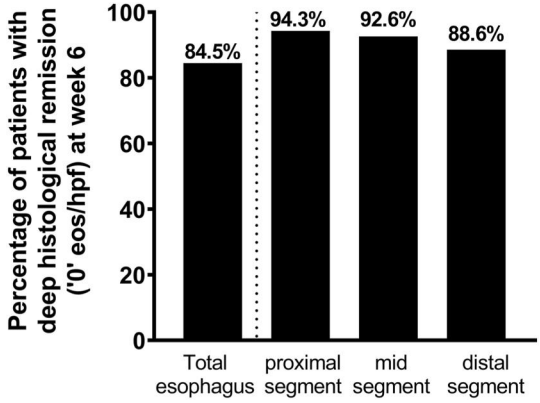

FIGURE 2 Deep histological remission (i.e., '0' eos/hpf) after 6 weeks of BOT 1 mg BID treatment stratified by the localization of the affected oesophagus segment BID, twice daily; BOT, budesonide orodispersible tablet; eos, eosinophils; hpf, high power field (400x)

inflammation is undoubtedly the key driver for fibrosis and stricture formation and most likely also increases the risk of future food impaction.[7–9] The remission rates observed in this trial, both for the composite endpoint as well as for its two components, were highly consistent with those of the previous phase 2 and 3 trials of BOT in adults with active EoE.[13,14] For instance, histological remission rates defined as <16 eos/mm^2 hpf (corresponding to <5 eos/hpf as described by Straumann et al. 2010[21]) were observed in 90% of patients after 6 weeks in this trial, in 100% of patients after 2 weeks in the double-blind phase 2 trial,[13] and in 90% of patients after 6 weeks in the double-blind phase 3 trial.[14] Even deep histological

TABLE 2 Efficacy endpoints at Week 6 (LOCF)

Efficacy endpoints	BOT 1 mg BID, *N* = 181
Clinico-histological remission, *n* (%)	126 (69.6)
Histological remission (<16 eos/mm^2 hpf)	
Total, n/N (%)	163/181 (90.1)
Distal oesophagus, n/N (%)	163/176 (92.6)
Mid oesophagus, n/N (%)	166/175 (94.9)
Proximal oesophagus, n/N (%)	169/175 (96.6)
Change in peak eos/mm^2 hpf	
Total oesophagus, mean (SD)/median [Q25%; Q75%], *p* value/N	−283 (271)/−210 [-325;-126], <0.0001/181
Relative (%) change from baseline, mean (SD/median [Q25%; Q75%], *p* value/N	−89.0 (42.5)/−100 [-100; −100]/<0.0001/181
Distal oesophagus, mean (SD)/median [Q25%; Q75%], *p* value/N	−201 (199.0)/−156 [-266;-83], <0.0001/177
Mid oesophagus, mean (SD)/median [Q25%; Q75%], *p* value/N	−189 (206.2)/−132 [-260;-41], <0.0001/180
Proximal oesophagus, mean (SD)/median [Q25%; Q75%], *p* value/N	−166 (231.8)/−107 [-212;-29], <0.0001/180
Peak number of eosinophils/mm^2 hpf	
Total oesophagus, mean (SD)/median [Q25%; Q75%]/N	12 (56)/0 [0; 0]/176
Distal oesophagus, mean (SD)/median [Q25%; Q75%]/N	10 (48)/0 [0; 0]/176
Mid oesophagus, mean (SD)/median [Q25%; Q75%]/N	7 (36)/0 [0; 0]/175
Proximal oesophagus, mean (SD)/median [Q25%; Q75%]/N	3 (19)/0 [0; 0]/175
Overall assessment of endoscopic activity, *n* (%)	
None	101 (55.8)
Mild	66 (36.5)
Moderate	14 (7.7)
Severe	-- (0)
Modified total EREFS score (0–9), mean (SD)	1 (1.3)
Mean (SD) change from wk 0 to wk 6 (LOCF)/*p* value/N	−3 (1.9)/<0.0001/176
Subscore inflammation (0–4), mean (SD)	1 (0.8)
Subscore fibrosis (0–4), mean (SD)	1 (0.8)
All subscores = '0', *n* (%)	72 (39.8)
Deep endoscopic remission,[a] *n* (%)	97 (53.6)
Resolutions of symptoms	
Dysphagia and odynophagia NRS (≤2), *n* (%)	136 (75.1)
Number of symptom-free days/week	
Dysphagia NRS (≤2), mean (SD)	6 (2.0)
Odynophagia NRS (≤2), mean (SD)	6 (1.7)
Total weekly EEsAI-PRO score ≤20, *n* (%)	89 (49.2)
Mean (SD) change from wk 0 to wk 6 (LOCF)/*p* value/N	−29 (21.4)/<0.0001/179
Patient's global assessment of EoE activity, (NRS 0–10), mean (SD)	2 (1.7)
Physician's global assessment of EoE activity, (NRS 0–10), mean (SD)	1 (1.6)
Deep clinical remission,[b] (dysphagia and odynophagia NRS '0'), *n* (%)	36 (19.9)
Deep endoscopic[a] and histological remission (<16 eos/mm^2 hpf), *n* (%)	94 (51.9)
Deep disease remission, *n* (%)	
(Deep clinical[b] and histological and deep endoscopic remission[a])	21 (11.6)

(Continues)

TABLE 2 (Continued)

Efficacy endpoints	BOT 1 mg BID, *N* = 181
Patient's global satisfaction with the treatment	
Extremely satisfied, *n* (%)	95 (52.5)
Satisfied, *n* (%)	66 (36.5)
Neither satisfied nor dissatisfied, *n* (%)	12 (6.6)
Dissatisfied, *n* (%)	2 (1.1)
Missing entries, *n* (%)	6 (3.3)

Note: All intra--group comparisons were performed using 2-sided, one-sample *t*-test, except for comparison of peak eos count, for which a 2-sided Wilcoxon signed-rank test was used.

[a]Deep endoscopic remission (modified EREFS subscores: fixed rings = '0' or '1', exudates = '0', furrows = '0', and edema = '0').

[b]Deep clinical remission (symptoms severity of '0' points on each 0–10 NRS for dysphagia and odynophagia, respectively on each day in the week prior to week 6.

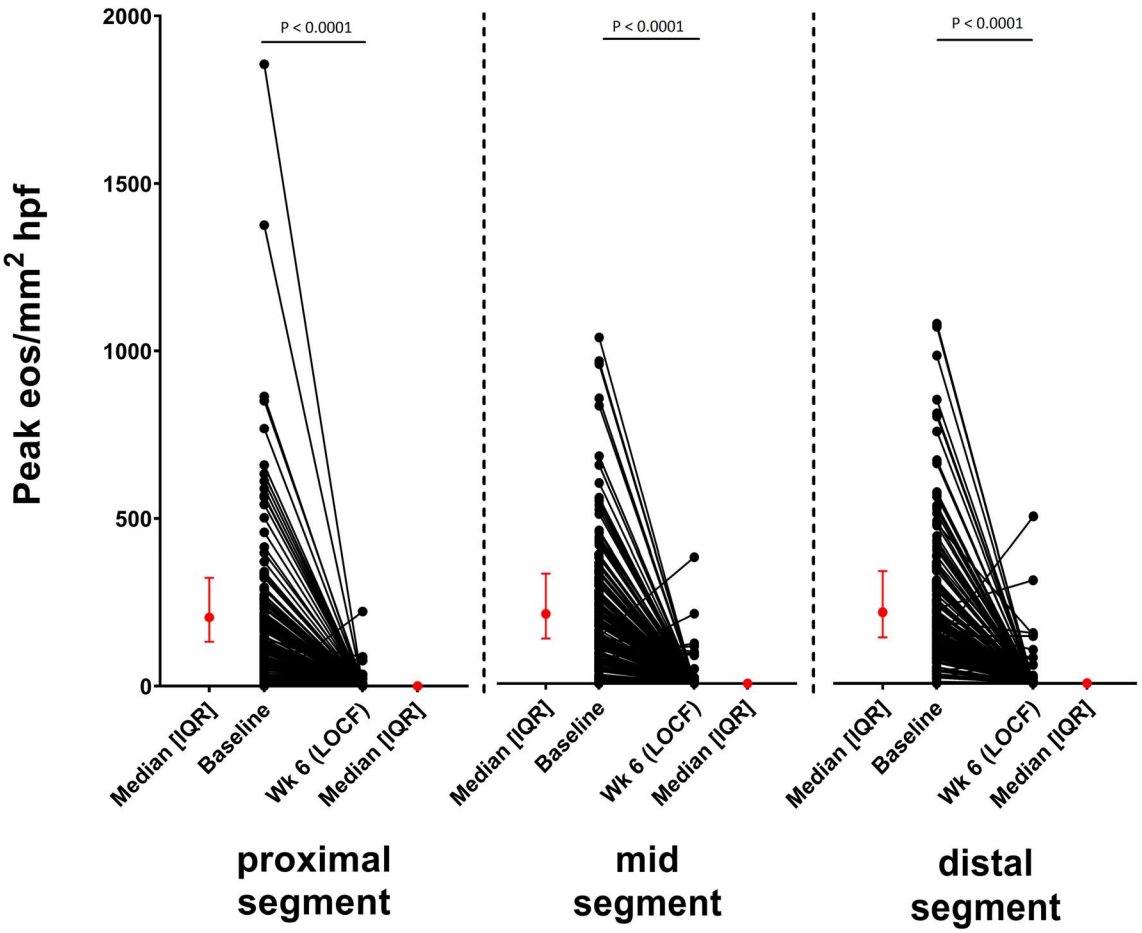

FIGURE 3 Individual pre- and post-treatment (with BOT 1 mg BID) peak eos/mm^2 hpf counts and median group values with IQR. BID, twice daily; BOT, budesonide orodispersible tablet; eos, eosinophils; hpf, high power field (400x); IQR, interquartile range; LOCF, last observation carried forward

remission, defined as '0' eos/hpf, was observed in 84.5% of patients in this trial, which was consistent with the rate of 89% in the previous double-blind phase 3 trial.[14]

As shown in the previous double-blind phase 2 and phase 3 trials, BOT 1 mg BID had similar anti-inflammatory effects in the entire oesophagus, independently of severity, localization or extent of inflammation, again underlining an optimal oesophageal targeting.[13,14]

The consistently high efficacy of BOT may be explained by the unique way of delivery of budesonide to the oesophagus. Once BOT is placed on the tongue, it stimulates the production of saliva via its

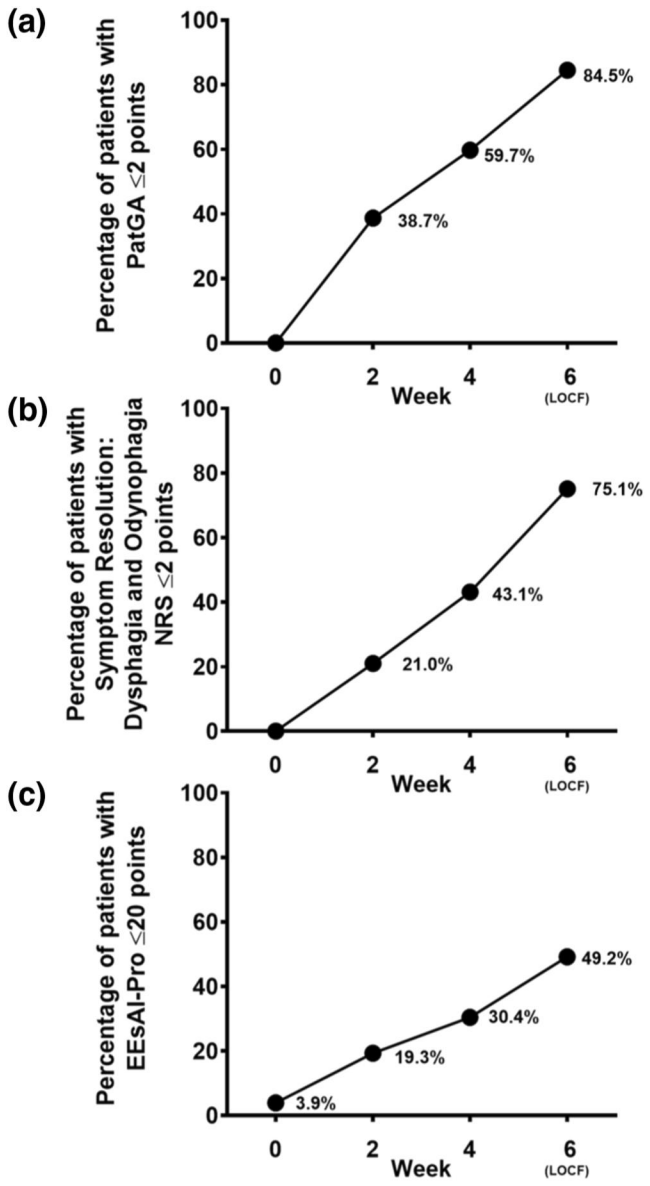

FIGURE 4 (a) Course of patient's global assessment of their EoE severity (PatGA) during treatment with BOT 1 mg BID Course of achieved clinical improvement defined as a Patient's Global Assessment of their EoE severity (PatGA) score of ≤2 on a 0–10 points numerical rating scale ('0' points: no EoE activity; '10' points: most severe EoE activity). (b) Course of clinical remission defined by symptom resolution during treatment with BOT 1 mg BID Course of achieved clinical remission defined as symptom resolution ≤2 on both 0–10 points numerical rating scales for dysphagia and odynophagia, respectively ('0' points: no dysphagia or odynophagia, respectively; '10' points: most severe dysphagia or odynophagia, respectively). (c) Course of clinical remission defined by Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) ≤20 points during treatment with BOT 1 mg BID

effervescence characteristics over several minutes. During this period, BOT completely disintegrates leading to slow release of budesonide into the saliva, which is continuously swallowed in small volumes.[15] The mucoadhesive properties of saliva may lead to an enhanced exposure and a prolonged contact time of budesonide to the oesophageal mucosa.

The particular mode of drug delivery with BOT might explain the high histological remissions rates in contrast to other corticosteroids suspensions which are usually ingested via a single swallow of a relatively large volume. For example, in the recent ORBIT trial, a phase 3 randomized placebo-controlled trial including 318 adolescent and adult EoE patients, a 12-week treatment with 2 mg BID of a budesonide oral suspension (10 ml at a concentration of 0.2 mg/ml), specifically developed for treatment of EoE, resulted in a histological remission rate (≤6 eos/hpf) of 53.1%.[25]

Obviously, comparison of such trials conducted in different patient populations are not permitted and head-to-head comparisons among different topical corticosteroids are lacking. However based on the available evidence, the latest network meta-analysis[26] concluded that BOT currently appears to be the most effective drug therapy for EoE in adults.

As in the previous double-blind phase 3 trial,[14] more patients in this trial achieved histological compared to clinical remission of EoE. Thus, nearly every patient in clinical remission at week 6 was also in histological remission, but not vice versa. With roughly 30% of patients with ongoing symptoms of oesophageal dysfunction amongst the histological remitters. This underlines the imperfect relationship between oesophageal symptoms and the biological activity of EoE.[27,28] Potential causes for these consistent observations may include residual mild oesophageal strictures, narrow oesophageal caliber underestimated by endoscopy or a decreased oesophageal distensibility.[29,30] For instance, the EREFS fibrosis subscore in this trial was only 1 at baseline and did not change significantly after 6 weeks. Thus, persistent mild fibrosis may have contributed to the discrepancy between histological and clinical response.

As indicated above, the assessment of the clinical improvement in EoE remains challenging, because oesophageal symptoms may not only depend on the histological disease activity, but also on the eating behavior of the patient. In this trial, we used a 10-point NRS for dysphagia and odynophagia which is a simple tool with obvious face validity. A similar 10-point Likert scale was recently confirmed to be responsive to assess dysphagia severity in EoE in clinical practice.[31] By using NRS, we measured a clinical remission rate of 75% at week 6 in this trial, which was slightly higher compared to the 58% at week 6 observed in the previous double-blind phase 3 trial.[14] This difference might simply be explained by the open-label design of this study. Clinical remission based on the NRS for dysphagia and odynophagia cut-off of ≤2 was consistent with all other clinical endpoints in this trial. For instance, the PatGA and PGA showed similar remission rates based on cut-offs of ≤2 on a scale from 0 to 10, while the EEsAI-PRO showed slightly lower remission rates based on the cut-off ≤20 on a 0–100 points scale. In contrast to NRS, EEsAI-PRO takes into account food avoidance, food modification and eating habits evaluating foods of eight different consistencies. In accordance with clinical improvement, both HRQoL tools (EoE-QoL-A and modified SHS) showed an improvement in HRQoL in all domains and items under BOT 1 mg BID.

TABLE 3 Health-related quality of Life

	Baseline Mean (SD)	Week 6 (LOCF) Mean (SD)	Change Mean (SD), *p* value
EoE-QoL-A (0–4)	*N* = 181	*N* = 181	*N* = 181
Overall (24 items)	2.5 (0.70)	3.1 (0.65)	0.5 (0.50), <0.0001
Eating/diet impact (10 items)	2.5 (0.93)	3.1 (0.81)	0.7 (0.75), <0.0001
Social impact	2.4 (0.93)	3.0 (0.90)	0.6 (0.82), <0.0001
Emotional impact	2.8 (0.80)	3.4 (0.65)	0.5 (0.52), <0.0001
Disease anxiety	2.2 (0.94)	2.5 (0.91)	0.4 (0.57), <0.0001
Swallowing anxiety	2.5 (0.94)	3.2 (0.82)	0.7 (0.73), <0.0001
Modified SHS (0–100)	*N* = 178	*N* = 181	*N* = 178
Symptom burden	57 (20.7)	16 (19.4)	−40 (23.6), <0.0001
Social function	45 (25.8)	15 (19.0)	−30 (24.5), <0.0001
Disease-related worry	53 (23.2)	28 (24.0)	−25 (23.9), <0.0001
General well-being	33 (21.8)	17 (18.3)	−15 (20.9), <0.0001

Note: All intra--group comparisons were performed using 2-sided, one-sample *t* test.

Abbreviations: EoE-QoL-A, Adult Eosinophilic Esophagitis Quality of Life (range of weighted average scores: 0–4): Higher scores denote better quality of life; LOCF, last observation carried forward; Modified SHS, Modified Short Health Scales (range of scores: 0–100): Lower scores denote better quality of life.

TABLE 4 Safety of induction treatment of eosinophilic oesophagitis with orodispersible budesonide tablets

Patients with at least one *n* (%)	BOT 1 mg BID *N* = 181
Treatment-emergent adverse events (TEAE)	112 (61.9)
Adverse drug reactions	60 (33.1)
Serious adverse events (SAE)[a]	3 (1.7)
TEAE leading to withdrawal from the study	6 (3.3)
Patients with treatment -emergent adverse drug reactions by System Organ Class and Preferred term (if of special interest)—no. (%)	
Eye disorders	1 (0.6)
Gastrointestinal disorders	17 (9.4)
General disorders and administration site conditions	3 (1.7)
Infections and infestations	23 (12.7)
Candidiasis overall:	23 (12.7)
Suspected symptomatic candidiasis	15 (8.3)
Histological confirmed candidiasis	15 (8.3)
Histological confirmed and symptomatic candidiasis	6 (3.3)
Investigations	5 (2.8)
Blood cortisol decreased	4 (2.2)
Musculoskeletal and connective tissue disorders benign, malignant and unspecified	1 (0.6)
Nervous system disorders	13 (7.2)
Dysgeusia	2 (1.1)
Psychiatric disorders	4 (2.2)
Reproductive system and breast disorders	1 (0.6)
Respiratory, thoracic and mediastinal disorders	9 (5.0)
Skin and subcutaneous tissue disorders	1 (1.0)

[a]All serious adverse events were assessed by the investigators as being not related to study drug intake.

On endoscopy, treatment with BOT 1 mg BID resulted in a significant improvement of the total modified EREFS mainly attributable to the 'inflammatory signs' subscore. As stated above, the EREFS fibrosis subscore was low at baseline and did not change significantly after 6 weeks. Notably, deep endoscopic remission (defined as modified EREFS subscores: fixed rings = '0' or '1', exudates = '0', furrows = '0' and edema = '0') was achieved in more than half of the patients.

We also evaluated the proportion of patients with deep disease remission, a term proposed by Greuter et al. in 2017.[22] They reported on 33 out of 351 patients (9.4%) who achieved deep disease remission after 89 weeks of treatment with low-dose budesonide suspension. In our study, deep disease remission was achieved in 11.6% of patients already after 6 weeks of treatment with BOT 1 mg BID.

This open-label trial also documented and confirmed the favorable safety profile of BOT 1 mg BID. In particular, the incidence of clinically manifested suspected local candidiasis assessed to be related to budesonide treatment was as low as 8.3%, which was consistent with the previous phase 3 double-blind induction of remission trial with BOT 1 mg BID.[14]

Strengths of our study include its large sample size and the high-quality study design, as this open-label induction trial was part of a multinational phase 3 programme where the same stringent outcome criteria were used as in the double-blind placebo-controlled induction trial including validated outcome measures such as EEsAI-PRO and EREFS.[14] Formal limitations of the study should be acknowledged, for example, the use of a non-validated symptom score (NRS) for the assessment of clinical remission and the lack of a placebo group.

In summary, BOT 1 mg BID is a highly effective and safe therapy for induction of disease remission in adult patients with active EoE.

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CONFLICT OF INTEREST

Stephan Miehlke reports receiving consulting fees from Celgene, Dr. Falk Pharma, EsoCap and Sanofi-Regeneron; receiving lecture fees from Dr. Falk Pharma and Vifor; receiving payment for the development of educational presentations from Dr. Falk Pharma; and serving as a board member for the European Society of Eosinophilic Oesophagitis (EUREOS). Christoph Schlag reports receiving consulting fees from Adare, Celgene, EsoCap, Dr. Falk Pharma and Sanofi-Regeneron; receiving lecture fees from Dr. Falk Pharma; and serving as a board member for EUREOS. Alfredo Lucendo reports receiving consulting fees from EsoCap, and Dr. Falk Pharma; receiving lecture fees from Dr. Falk Pharma; and serving as a board member for EUREOS. Luc Biedermann reports receiving consulting fees from Calypso Biotech; Esocap; Vifor, and Sanofi-Regeneron; receiving lecture fees from Dr. Falk Pharma; Sanofi-Aventis; and serving as a board member for EUREOS. Cecilio Santander Vaquero reports receiving lecture fees from Allergan and receiving payment for the development of educational presentations from Laborie. Christoph Schmoecker reports no conflict of interest. Jamal Hayat reports receiving lecture fees from Dr. Falk Pharma. Petr Hruz reports no conflict of interest. Jamal Hayat reports receiving consulting fees from Dr. Falk Pharma; and receiving lecture fees from Dr. Falk Pharma. Constanza Ciriza de los Rios reports receiving consulting and/or lecture fees from Allergan and Casen Recordati. Albert Jan Bredenoord reports receiving research funding from Nutricia, Norgine, SideSleepTechnologies and Bayer; receiving lecture and/or consulting fees from Laborie, Arena, EsoCap, Diversatek, Medtronic, Dr. Falk Pharma, Calypso Biotech, Thelial, Robarts, Reckett Benkiser, Regeneron, Celgene, Bayer, Norgine, AstraZeneca, Almirall, Arena and Allergan. Michael Vieth reports receiving lecture fees from Dr. Falk Pharma, Janssen-Cilag, Malesci, Menarini, Olympus, Shire. Alain Schoepfer reports receiving consulting fees from Abbvie, Adare, Celgene, Dr. Falk Pharma, Janssen-Cilag, MSD, Pfizer, Receptos, Regeneron, Vifor and Sanofi-Regeneron; receiving lecture fees from Abbvie, Celgene, Dr. Falk Pharma, Pfizer, Receptos, Regeneron, and Vifor; and serving as a board member for The International Gastrointestinal Eosinophil Researchers (TIGERS). Stephen Attwood reports receiving consulting fees from Dr. Falk Pharma, EsoCap, AstraZeneca, and Reckitt Benkiser; receiving lecture fees from Dr. Falk Pharma, Medtronic; receiving payment for the development of educational presentations from Dr. Falk Pharma. Ralph Mueller reports being an employee of Dr. Falk Pharma GmbH. Sarah Burrack reports being an employee of Dr. Falk Pharma GmbH. Roland Greinwald reports being an employee of Dr. Falk Pharma GmbH. Alex Straumann reports receiving consulting fees from Allakos, AstraZeneca, EsoCap, Dr. Falk Pharma, Gossamer, GSK, Receptos-Celgene and Regeneron-Sanofi; receiving lecture fees from Dr. Falk Pharma and Vifor; receiving payment from Dr. Falk Pharma for the development of educational presentations; receiving payment from AstraZeneca for serving as member of IDMC (independent data monitor committee); and serving as a board member for EUREOS and TIGERS.

AUTHOR CONTRIBUTIONS

Stephan Miehlke, Alfredo J. Lucendo and Alex Straumann: Development of the study protocol, patient recruitment, data analysis and interpretation, manuscript preparation. Michael Vieth: Development of the study protocol and central pathologist. Stephen Attwood and Alain Schoepfer: Development of the study protocol and manuscript preparation. Christoph Schlag, Luc Biedermann, Cecilio Santander Vaquero, Christoph Schmoecker, Jamal Hayat, Petr Hruz, Constanza Ciriza de los Rios and Albert Jan Bredenoord: Patient recruitment. Ralph Mueller and Roland Greinwald: Development of the study protocol, data analysis and interpretation, support for manuscript preparation. Sarah Burrack: Data analysis and interpretation, support for manuscript preparation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available from the European Medicines Agency homepage as soon as the Clinical

Study Report will be available in the public domain in a redacted form as part of the transparency initiative for products achieving marketing authorization via a centralized procedure.

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REFERENCES

1. Lucendo AJ, Molina-Infante J, Arias Á, Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017;5:335–58.
2. Navarro P, Arias A, Aria-Gonzalez L, Laserna-Mendieta EJ, Ruiz-Ponce M, Lucendo AJ. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2019;49:1116–25.
3. Sengupta N, Tapper EB, Corban C, Sommers T, Leffler DA, Lembo AJ. The clinical predictors of aetiology and complications among 173 patients presenting to the Emergency Department with oesophageal food bolus impaction from 2004-2014. Aliment Pharmacol Ther. 2015;42:91–8.
4. Lenz CJ, Leggett C, Katzka DA, Larson JJ, Enders FT, Alexander JA. Food impaction: etiology over 35 years and association with eosinophilic esophagitis. Dis Esophagus. 2019;32:doz010.
5. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology. 2018;154:319–32.
6. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon H-U. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology. 2003;125:1660–9.
7. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013;145:1230–6.
8. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, Smout AJPM, Bredenoord AJ. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol. 2018;113:836–44.
9. Shaheen NJ, Mukkada V, Eichinger CS, Schofield H, Todorova L, Falk GW. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. Dis Esophagus. 2018;31:doy015.
10. Lucendo AJ, Arias-Gonzalez L, Molina-Infante J, Arias Á. Systematic review: health-related quality of life in children and adults with eosinophilic oesophagitis-instruments for measurement and determinant factors. Aliment Pharmacol Ther. 2017;46:401–9.
11. Hirano I, Chan ES, Rank MA, Sharaf RN, Stollman NH, Stukus DR, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology. 2020;158:1776–86.
12. De Heer J, Miehlke S, Rösch T, Morgner A, Werner Y, Ehlken H, et al. Histologic and clinical effects of different topical corticosteroids for eosinophilic esophagitis: lessons from an updated meta-analysis of placebo-controlled randomized trial. Digestion. 2021;102:377–85.
13. Miehlke S, Hruz P, Vieth M, Bussmann C, von Arnim U, Bajbouj M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut. 2016;65:390–9.
14. Lucendo AJ, Miehlke S, Schlag C, Vieth M, von Arnim U, Molina-Infante J, et al. Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomized placebo-controlled trial. Gastroenterology. 2019;157:74–86.
15. Miehlke S, Lucendo AJ, Straumann A, Bredenoord AJ, Attwood S. Orodispersible budesonide tablets for the treatment of eosinophilic esophagitis - a review of the latest evidence. Ther Adv Gastroenterol. 2020;13:1756284820927282.
16. Liacouras CA, Furuta GT, Hirano I, Attwood SE, Bonis PA, Burks AW, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:3–20.
17. Straumann A, Lucendo AJ, Miehlke S, Vieth M, Schlag C, Biedermann L, et al. Budesonide orodispersible tablets maintain remission in a randomized, placebo-controlled trial of patients with eosinophilic esophagitis. Gastroenterology. 2020;159:1672–85.
18. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology. 2014;147:1255–66. e21.
19. Bajaj S, Taft T, Keefer L, Gonsalves N, Hirano I. Validity, usability, and acceptability of the eosinophilic esophagitis quality of life scale for adults (EoE-QOL-A). Gastroenterology. 2012;142:S–434.
20. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013;62:489–95.
21. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010;139:1526–37.
22. Greuter T, Bussmann C, Safroneeva E, Schoepfer AM, Biedermann L, Vavricka SR, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concep. Am J Gastroenterol. 2017;112:1527–35.
23. Dellon ES, Gupta SK. A conceptual approach to understanding treatment response in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2019;17:2149–60.
24. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20:109–17.
25. Hirano I, Collins MH, Katzka DA, Mukkada VA, Falk GW, Morey R, et al. Budesonide oral suspension improves outcomes in patients with eosinophilic esophagitis: results from a phase 3 trial. Clin Gastroenterol Hepatol. 2021:S1542-3565(21)00456-0.
26. Rokkas T, Niv Y, Malfertheiner P. A network meta-analysis of randomized controlled trials on the treatment of eosinophilic esophagitis in adults and children. J Clin Gastroenterol. 2021;55:400–10.
27. Larsson H, Norder Grusell E, Tegtmeyer B, Ruth M, Bergquist H, Bove M. Grade of eosinophilia versus symptoms in patients with dysphagia and esophageal eosinophilia. Dis Esophagus. 2016;29:971–6.
28. Safroneeva E, Straumann A, Coslovsky M, Zwahlen M, Kuehni CE, Panczak R, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology. 2016;150:581–90.
29. Gentile N, Katzka D, Ravi K, Trenkner S, Enders F, Killian J, et al. Oesophageal narrowing is common and frequently underappreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther. 2014;40:1333–40.
30. Nicodeme F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2013;11:1101–7.

31. Reed CC, Wolf WA, Cotton CC, Dellon ES. A Visual Analogue Scale and a Likert scale are simple and responsive tools for assessing dysphagia in eosinophilic oesophagitis. Aliment Pharmacol Ther. 2017;45:1443–8.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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