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REVIEW



# Drug treatment strategies for eosinophilic esophagitis in adults

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**ABSTRACT**

**Introduction:** Eosinophilic esophagitis (EoE) is a clinical and pathological disorder, characterized by symptoms of esophageal dysfunction, and eosinophil-predominant inflammation restricted to the esophagus. Treatment outcomes include symptomatic remission, histological and endoscopic normalization and improving quality of life. Besides dietary modifications and endoscopic dilation, drugs available are swallowed topical corticosteroids (STCs) with reduced bioavailability and proton pump inhibitors (PPI).

**Areas covered:** Herein, the authors review the current treatment strategies for EoE in adults, providing the reader with their expert perspectives. The authors give discussion to the value of PPIs as a first-line therapy for EoE, in addition to the use of STCs. The current development of new formulations of STCs targeting the esophagus and novel therapies aimed at blocking molecular pathways are also discussed. Finally, the authors briefly look at the value of monoclonal antibodies targeting IL-5RA, IL-13, IL-4 or Siglec8, and oral S1PR agonists to the treatment of EoE.

**Expert opinion:** Viscose formulations of STC designed to coat the esophagus and new effervescent orodispersible tablets provide increased effectiveness at low doses. Investigational therapies that target several Th2-associated diseases seem useful in EoE. Comparative effectiveness and cost-utility analyses will help to position them in a complex therapeutic scenario.

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## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic disease characterized histologically by eosinophilic inflammation restricted to the esophagus and clinically by symptoms of esophageal dysfunction that vary widely according to patient's age[1,2]. Thus, younger children, unable to report dysphagia effectively, present with irritability and several of eating disorders, including failure-to-thrive or food aversion; later symptoms consist on regurgitation, vomiting, and both chest and abdominal pain, mimicking gastroesophageal reflux disease (GERD). In children aged 11 years and older, EoE symptoms mainly consist in dysphagia and food impaction, which are also the predominant symptoms in adults [3].

Over the last 3 decades, the prevalence of EoE has increased exponentially, currently affecting at least 1 in every 1,000 inhabitants in North America and Europe [4–6]. Today it is the main cause of symptoms of chronic or intermittent esophageal dysfunction in children, adolescents, and young adults, and the second form of chronic esophagitis after GERD. Consequently, the health-care costs associated with EoE have become vast, due to quite common diagnostic delay, the dependence from endoscopy with biopsies to achieve a diagnosis of EoE and to monitor response to therapy, and the costs of new drugs. Recently, it has been estimated that the mean annual cost per adult EoE patient reach $ 2,300 in the United States (US) [7]. In children, this cost increases considerably up to $ 4,001 per year, far exceeding the cost of care for Crohn's disease ($ 985) and celiac disease ($ 856) [8]. Although rare, the average cost of each hospital admission associated with EoE in the US has been calculated to be $ 5,135 per patient, and the number of admissions increased by 70% over the period 2010–2016, to represent 13 for every 100,000 hospitalizations, at an annual cost of US $ 24 million [9].

Despite the above, EoE remains undetected in many settings [10], which contributes to a considerable diagnostic delay [11]. The natural course of EoE consists of a long-lasting (probably life-long) chronic inflammation in the esophagus, which can promote collagen deposition beneath the esophageal epithelium, leading to fibrosis in the lamina propria and in deeper layers, and formation of rigid fibrotic strictures. The phenomena of fibrous remodeling appear to be proportional to the time of active disease without a diagnosis, and therefore, without effective treatment, and increases the risk of complications [12]. Most common complications consist of mucosal tears, produced either spontaneously while trying to dislodge impacted food or following endoscopic procedures. However, occasionally they can reach esophageal perforations, which is potentially severe may require esophageal surgery or stenting. Esophageal perforation has been occasionally described as the initial presentation of EoE [13,14].

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**Article highlights**

- Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease, mainly triggered by exposure to dietary antigens and characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation restricted to the esophagus.
- Current therapeutic goals in eosinophilic esophagitis (EoE) in adults include symptomatic remission, histological normalization with (near) disappearance of eosinophilic inflammation, normalization of endoscopic features (especially the fibrotic effects of long-lasting inflammation), and restoring and maintaining adequate quality of life.
- Available anti-inflammatory therapies able to induce and maintain remission in EoE currently include dietary modifications, proton pump inhibitors and swallowed topical corticosteroids. In case of esophageal stricture or narrowing, they should be combined with endoscopic dilation. As the disease recurs after treatment cessation, long-term maintenance with the lowest effective dose of diet is required.
- Since there are no approved drugs to treat EoE in many setting, patients are usually treated with off-label preparations of topical corticosteroids, administered as nebulizer solutions, nasal drops, or metered-dose inhalers, which should be swallowed instead of inhaled, or by mixing the compound with different vehicles.
- Novel formulas of topical corticosteroids and devices designed to coat the esophageal mucosa and to deliver the medication into the esophagus increase the effectiveness in treating EoE. Budesonide orodispersible tablets are now available in several European countries to treat adult EoE patients.
- Monoclonal antibodies imported from other Th2-mediated allergic conditions that target interleukin (IL)-4, IL-13 and the α subunit of the IL-5 receptor (IL-5Rα) are now being investigated for EoE in late-phase clinical trials.
- Lirentelimab, a Siglec-8 blocker able to induce eosinophil apoptosis, and etrasimod, a S1PR agonist, are promising therapies to be incorporated into clinical practice.

As symptoms usually persist or intensify over time, as the fibrotic sequelae of EoE develop [15], patients frequently adopt adaptive coping behaviors, such as drinking water with every meal, becoming slow and careful eaters, and avoid situations where there is a risk of food impaction and associated anxiety, including dining out or social situations that revolve around food [16]. This can lead to social isolation and patients become hyper-vigilant around food [17] and suffer from mental distress [18] or psychiatric comorbidity [19]. As a result, EoE impairs health-related quality of life (HRQoL) of patients [20,21]. Therefore, improving HRQoL is now considered a primary outcome of any new drug therapy developed for EoE.

The pathophysiology of EoE is sensitive to a non-IgE-mediated Th2-type immune response [22] against certain dietary antigens present in the esophageal lumen. This response triggers inflammatory cascades mediated by cytokines, such as interleukin (IL)-4, IL-5 and IL-13 [23], which terminate in the activation of eosinophils as end effectors of inflammation [24]. The cytotoxic content released from eosinophil granules in an attempt to neutralize triggering antigens [23] causes mucosal damage and esophageal symptoms. As a particular form of food allergy [25], the elimination of food triggers currently represents the only therapy that targets the cause of EoE, able to induce and maintain its remission [26]. Several dietary strategies have been used to treat EoE, with empiric food elimination being the only feasible approach, because no food allergy test is able to accurately predict or identify food trigger(s) for EoE [26]. However, recent studies have shown that long-term adherence to a severely restricted diet is low, a fact that, coupled with the need for repeated endoscopy to verify disease remission and assess recurrence after dietary challenges, acts as a deterrant for patients who are not particularly motivated.

Due to the above, the pharmacological treatment of EoE has gained popularity in recent years, and despite specifically approved drugs to treat patients with EoE still not being available in many settings, this is one of the areas of more intense development in the understanding of this disease. Firstly used to treat EoE in 1998 [27], swallowed topical corticosteroids (STC) are currently used to induce histological remission of the disease [28], and novel formulations designed to coat the esophageal inner surface also provide long-term benefit [29]. By acting through anti-inflammatory effects, independent of their activity on gastric acid secretion [30,31], proton pump inhibitors (PPIs) have been also shown an effective first-line therapy for EoE [32] able to achieve [33] and maintain [34–36] clinical and histological remission in around 50% of patients. Finally, esophageal dilation may provide symptom relief up to 95% of patients with a reduced esophageal caliber [37]. As endoscopic dilation is a mechanical procedure with no effect on the mucosal inflammation, it usually needs to be used together with effective diet or drug-based anti-inflammatory therapies in patients with fibrostenotic esophageal features (such as esophageal rings of narrow caliber esophagi) or persistent dysphagia/food impaction, even though they are under an effective drug- or diet-based anti-inflammatory therapy [38].

This article provides a summary on the effectiveness and limitations of current pharmacological options for treating EoE in adults. Drug therapies under investigation are also discussed.

## 2. The evolving landscape of therapeutic goals in eosinophilic esophagitis

Since its initial descriptions almost 3 decades ago [39,40], therapy in EoE has evolved more than any other aspect of the disease. The effectiveness of a therapy has been mostly defined as inducing and maintaining symptomatic improvement or remission, and controlling eosinophilic inflammation [41]. However, the lack of validated definitions for clinical remission or improvement, as well as differences in the threshold of eosinophil density considered to define histological activity or remission, provided evident heterogeneity in results from therapy in EoE literature [42]. Disease-specific instruments developed recently to capture disease-specific symptoms of EoE in children [43] and adults [44,45], which are not assessable with standard instruments. The EoE Activity Index (EEsAI) is an adult patient-reported outcome (PRO) instrument (recall period of 7 days) that quantifies patient difficulties with dietary or behavioral modifications to facilitate the ingestion of different food consistencies [45]. After assessing several cutoff values, the EEsAI index is not sufficient enough to predict histological or endoscopic remission of EoE (receiving operation curve analysis with area under the curve of 0.60 to

0.67 to predict histological and endoscopic remission, respectively) [46]. The Dysphagia Symptom Questionnaire (DSQ) is a validated measure of dysphagia in adolescent and adult patients with EoE that comprises three questions on the presence and severity of EoE dysphagia [44]. A minimum of 8 entries in a 14-day period are required to provide the DSQ score, which has been shown to correlate weakly, but significantly, with a change in peak eosinophil count in esophageal biopsies [47]. However, a change in DSQ score did not correlate with other histological and endoscopic outcomes in patients with EoE treated with budesonide or fluticasone [48]. As for children, the Pediatric EoE Symptom Score (PEESS® v2.0) was developed and validated to measure relevant outcomes that children with EoE and their families identified as important, which include four major domains: dysphagia, gastrointestinal reflux disease (GERD), nausea/vomiting, and pain [43]. PEESS® v2.0 score did not correlate significantly with eosinophil levels in esophageal biopsies obtained in the upper and lower esophageal thirds [49]. These instruments are being used in clinical trials but have not yet been applied in real-world practice [50]. Assumptions about EoE activity based solely on symptoms should be avoided.

Evidence shows that symptoms and the density of eosinophilic inflammation in esophageal biopsies correlated poorly in patients with EoE [46,51]. The involvement of the deepest layers of the esophagus [52], the reduction in the distensibility of the organ as a result of fibrosis [53], the development of long-term adaptive behaviors to avoid symptoms [54], or even the development of hyper-vigilance and anticipatory anxiety [17] and other psychological changes after long-lasting symptoms [55] could contribute to explaining this discrepancy between clinical and biological activity in EoE, which has also been observed in other inflammatory gastrointestinal diseases [56]. As a result, endoscopic biopsies continue to be essential for the evaluation of activity in patients with EoE.

With respect to histopathological outcomes, both mean and peak eosinophil counts on esophageal biopsies have been considered as measures for disease activity by different researchers in the early EoE literature, with peak eosinophil count now being the definitive criterion for evaluating EoE activity. A cut-off point of 15 eos/hpf had a sensitivity of 100% and a specificity of 96% for diagnosis of eosinophilic esophagitis [57]. Although an histological cutoff of <15 eosinophils/high-power field (hpf) is appropriate to define treatment response in clinical practice, since it identifies most patients with symptom and endoscopic improvements [58], stringent histological thresholds <6 eosinophils/hpf have been requested by regulatory authorities [59] and are now defined in most trials assessing drugs for EoE. As the size of an hpf (i.e. 400x full magnification in a light microscope) is not a standard measurement, but varies between different manufacturers, it is recommended to also report the exact hpf size in square millimeters. Additional histological findings accompanying eosinophilic infiltration are assessed through the EoE Histology Scoring System (HSS) [60], which evaluates peak eosinophil count and 7 additional individual histological features, potentially overcoming the limitations of assessing eosinophil counts alone [61]. A number of randomized controlled trials (RCT) have used the EoE-HSS to assess its potential advantages over simply counting cells; however, a recently published study aimed at comparing the responsiveness of the EoE-HSS with that of a simple peak eosinophil count demonstrated that both measures performed; similarly, although EoE-HSS correlated better with changes in overall histological activity [62].

A number of esophageal abnormalities have been identified in patients with EoE, with a significantly variable frequency among studies [63]. These abnormalities were systematized into eight categories to create the EREFS scoring system [64], an acronym for Rings, Exudates, Edema, Furrows, and Stricture. Other features, such as a narrow caliber esophagus, are not always captured in the EREFS and commonly are underestimated in endoscopic examinations when compared to barium esophagography [65]. Despite the EREFS composite score (but not individual endoscopic signs) only correlating weakly with peak eosinophil counts, and its predictive value for disease activity being demonstrated as insufficient for clinical use [66,67], EREFS standardizes the assessment of EoE activity. It is now used as a relevant endpoint in both RCT and observational studies, which report separately both inflammatory and fibrotic components of the EREFS score.

Regulatory agencies have encouraged efforts to reach agreements on validated definitions for clinical, endoscopic, and histopathologic remission of EoE, and to achieve homogeneity in reporting treatment outcomes to enable comparisons between different options [68]. To achieve this goal, a multidisciplinary, international collaboration between multiple stakeholder groups recently developed a proposal to standardize outcome reporting in therapeutic studies of pharmacological and dietary interventions for patients with EoE [69]. They proposed four critical outcome domains: histopathology, endoscopy, symptoms, and HRQoL determined with disease-specific instruments. In addition, experts also proposed other optional important domains to be further evaluated in upcoming trials, with esophageal distensibility measured by endoscopic functional lumen image probe (endoFLIP) being the best at present.

The performance of each of the variety of drugs already available or currently under development for the different treatment goals varies widely, and will be discussed in the following sections of this article.

## 3. Proton pump inhibitor therapy for EoE: more than blocking acid secretion

In the period between the publication of the first [70] and last clinical guidelines [1] for this disease, the position of PPI in the management of EoE has been one of the most controversial points moving from being a diagnostic tool to becoming a true therapeutic option [32]: Initially, a 'PPI trial' was used to distinguish GERD and EoE, with remission of eosinophilic inflammation indicating GERD as the cause of esophageal eosinophilia and the failure of PPI treatment as a diagnostic for EoE [70]. The demonstration of patients who responded to PPI but had no evidence of reflux in esophageal pH-metry [71] undermined this simple dichotomy, giving rise to a third

condition initially classified as 'PPI-responsive esophageal eosinophilia (PPI-REE)' [72]. Patients with PPI-REE were demonstrated as being identical to those with EoE in terms of clinical, endoscopic, and histological presentation [30], as well as at a molecular and genetic level [73,74], except because the disease in the former was resolved with PPIs. However, patients with response to PPIs could also achieve remission after other alternative therapies [75,76]. Accordingly, the most recent diagnostic guidelines have eliminated the requirement for a PPI trial and have instead placed PPIs in the therapeutic algorithm [1,2]. Currently, PPIs represent the most frequently prescribed first-line therapy for EoE in patients of all ages [77–79].

Beyond and independently of their ability to inhibit gastric acid secretion, the effectiveness of PPIs in EoE relies on a direct anti-inflammatory effect by downregulating esophageal gene expression of major Th2 cytokines (i.e. IL-5 and IL-3) and chemokines (eotaxin-3/CCL26) which lead to eosinophil accumulation; similar to patients treated with topical corticosteroids [74]. Among responders, PPI therapy restores the integrity of the damaged esophageal mucosa [80] and reverses the inflammatory transcriptome [73].

Data on the effectiveness of PPI therapy to improve symptoms and eliminate EoE eosinophilic inflammation has been provided by two randomized trials that compared esomeprazole (40 mg once daily for 8 weeks) with aerosolized fluticasone propionate (440 mcg by mouth twice a day) [81,82]. Overall 50% of patients achieved peak eosinophil counts <15 eosinophils/hpf, with no significant differences with fluticasone. In addition, 33% of patients treated had <5 to <7 eosinophils/hpf after treatment with esomeprazole. In terms of frequency of symptoms, dysphagia improved in the majority of patients with no difference between the two treatment arms; however, no validated instruments to assess dysphagia in EoE patients were used in these studies.

However, most evidence to support the effectiveness of PPI therapy to treat EoE has been provided by observational studies, predominantly based on prospective and retrospective case series, and involving pediatric and adult patients. A systematic review with meta-analysis published in 2016 summarized the results of the 33 studies available up to this point [33] and provided evidence that PPIs given at double doses (i.e. omeprazole 40 mg daily of equivalent) led to histological remission (defined as <15 eos/hpf) in 50.5% (95% confidence interval [CI] = 42.2–58.7%) of patients, irrespective of patient age, study design or the presence of pathologic acid esophageal exposure by pH-monitoring. As for clinical benefits, any symptomatic improvement was reported in 60.8% (95% CI = 48.38–72.2%) of patients, generally with non-validated scores. After the publication of this meta-analysis, subsequent studies merely confirmed these data: An analysis of EoE CONNECT, a European multicenter registry [83] with over 630 EoE patients of all ages, recruited mostly prospectively, showed double doses of PPI achieved eosinophil density below 15 eosinophils per high-power field in 48.8% of patients (with 37.9% achieving <5 eosinophils/hpf) and a decreased symptom score (measured with a non-validated but responsive score) in 71.0% of patients. Notably, prolonging treatment length from 8 to 12 weeks increased the odds of achieving remission (Odds ratio 2.7; 95% CI, 1.3–5.3). No differences were noted when a range of PPI drugs were compared at equivalent doses, but patients with a stricturing EoE phenotype tended to respond worse to PPI therapy. Similar results have been recently provided by a second large retrospective cohort of patients from Denmark [84].

The effectiveness of PPIs in maintaining remission of EoE among patients who initially responded to them was subsequently assessed: Seventy-eight percent of a prospectively recruited series of children remained in remission at half the dose used for induction 1 year later [35]. For adults, half the initial PPI dose maintained clinical and histologic remission in at least 75% of patients after at least 1 year of follow-up [34,36]; in most relapsing patients, escalation to initial doses recovered remission. The EoE CONNECT registry also documented that a reduced dose of PPI from that used for induction was effective in maintaining clinical and histological remission of EoE in 69.9% patients. Evidence-based guidelines published in 2017 recommended PPI as an inexpensive, accessible, convenient, and moderately effective first-line therapy for EoE

In response to recently proposed treatment goals for EoE [69], the ability of PPI to improve endoscopic features of fibrosis has been recently demonstrated in a prospective series of 166 patients [85]: Short-term treatment with PPIs significantly reduced total EREFS scores in responding patients, as well as the presence of rings and strictures. Patients who achieved deep histological remission (<5 eosinophils/hpf) had a greater reduction in the total EREFS score. An increase of esophageal distensibility was demonstrated in a sub-cohort of these patients. To date, no study has evaluated in a structured way the impact of PPI treatment on the HRQoL of patients with EoE.

No safety concerns have been reported at present for PPI therapy in EoE. It is generally considered safe, despite recent concerns around the potential complications with long-term use [86,87]. This is likely to have been overestimated by the presence of confounding factors in most studies, thus generating an unnecessary controversy [88]. Standard doses used between 5 and 12 years in adults with GERD have shown no significant side effects [89], but definitive data on the long-term safety of PPI therapy in children has yet to be provided.

## 4. Beyond PPI: The potential of potassium-competitive acid blockers to treat EoE

Potassium-competitive acid blockers (P-CAB) are a new class of antisecretory drugs that, compared to PPIs, are capable of providing longer-lasting acid suppression, early onset of action, improved control of nocturnal acid secretion, and reversible blockade of the proton pump (H+, K+-ATPase α subunit) [90]. At present, P-CAB are exclusively marketed in Japan (vonoprazan) and South Korea (rebaprazan). Vonoprazan fumarate (the best-studied drug in this class) has provided evidence of superiority compared to PPIs in maintaining control of reflux esophagitis and improving eradication rates of *Helicobacter pylori*[91]. New data also indicate that vonoprazan could be effective in treating patients with EoE.

The genetic signature in biopsy samples obtained from patients with PPI-responsive EoE compared to non-PPI response EoE controls found that the only gene with significant differential expression was *KCNJ2* (Potassium inwardly-rectifying channel, subfamily J, member 2/Kir2.1) [73]. According to recent publications, standard doses of vonoprazan provided similar effectiveness to PPIs in a retrospective cohort of 118 Japanese patients with EoE [92]. In contrast, vonoprazan resulted superior to PPI in another retrospective Japanese EoE series, in which it was given to 20 EoE patients who were nonresponsive to PPI therapy, and 12 showed clinical and histological remission [93]. Safety and effectiveness of P-CAB in Western populations still needs to be assessed.

## 5. Topical corticosteroids: The keys to act on the esophageal mucosa

Topically administered corticosteroids with reduced bioavailability (beclomethasone and budesonide), swallowed instead of inhaled, were initially used to treat EoE in a small series of four children in 1998, shortly after the description of the disease. They were demonstrated to be as effective as orally administered systemic steroids in inducing histological remission and symptomatic improvement of the disease [27], but with significantly less side effects. Later, aerosolized fluticasone propionate [94,95] and mometasone furoate [96] also provided evidence of effectiveness in treating EoE. However, all drugs initially used were off-label preparations of topical corticosteroids, marketed for rhinitis or bronchial asthma, in the form of nasal drops, nebulizer solutions or metered-dose inhalers, which were to be swallowed instead of inhaled [97].

The initial studies used slightly different criteria to define histological remission, but both budesonide and fluticasone propionate were demonstrated to be superior to placebo in reducing peak eosinophil counts below either 15 cells/hpf (odds ratio = 24.6, 95%, CI = 7–86.8) [98], and <6 eosinophils/hpf (odds ratio = 35.82, 95% CI = 14.98–85.64), and in restoring an endoscopically normal esophagus in patients with active EoE (odds ratio = 3.51, 95% CI = 1.47–8.36) [99]. However, symptomatic remission could not be achieved in all cases, as several trials used unstructured or non-validated measurement instruments. Details on doses and administration modes of topical steroids in EoE are provided in Table 1

Table 1. Swallowed topical steroid initial dosing to treat eosinophilic esophagitis in adults.

| Drug | Induction dosing (usually divided doses) | Maintenance dosing (usually divided doses) |
|---|---|---|
| Fluticasone propionate[a,b] | 1760 µg/day | 880–1760 µg/day |
| Fluticasone propionate suspension[c] | 2000 – 4000 µg/day | not reported |
| Budesonide viscous solution[d] | 2–4 mg/day | 2 mg/day |
| Budesonide orodispersible tablet[e] | 2 mg/day | 1 mg/day |
| Mometasone furoate | 800 µg/day[g] | not reported |
| Beclomethasone dipropionate[f] | 320 µg/day | not reported |

[a]If an inhaler is used, the patients should be instructed to puff the medication into their mouth during a breath hold.
[b]Regardless of the form of administration (nebulized or swallowed nasal drops), patients should fast at least 30–60 min after medication in order to minimize esophageal drug clearance.
[c]The medication was formulated as a viscous suspension by mixing powdered fluticasone with a hydroxypropyl methylcellulose gel at a concentration of 1 mg/8 mL.
[d]Oral viscous budesonide preparation consists of mixing 1–2 mg budesonide with 5 mg of sucralose or similar.
[e]Available in several European countries, the daily dose is divided into two doses.
[f]Provided at inhalation aerosol 80 µg per puff, 2 puffs swallowed twice a day

### 5.1. Viscous formulations of corticosteroids: targeting the mucosa

Subsequently, viscous formulas of budesonide were developed by mixing this compound in different solutions as a vehicle for delivering medication into the esophagus [100]. The literature describes a wide variety of vehicles, which, mixed with budesonide, were used to treat patients with EoE, with variable efficacy [101]. Among those, one typical option was mixing liquid budesonide intended for nebulized administration with sucralose, or with a hypoallergenic food powder (Neocate Nutra) to create a slurry consistency [102,103]; however, patients (or their parents) have also mixed budesonide with cocoa mix, pear sauce, xanthan gum, and rice cereal [103].

The potency of action of budesonide and fluticasone is comparable, but the method used to deliver the drug over the esophageal mucosa has been shown to be essential to ensure its therapeutic effect. A RCT that compared oral viscous budesonide to nebulized budesonide given at the same dose, demonstrated that the former provided better coverage of the internal esophageal surface and longer contact time between the drug and the mucosa, which resulted in a greater therapeutic effect, in the form of a higher reduction in peak eosinophil counts in mucosal biopsies and a greater proportion of patient with a normal endoscopic appearance of the esophagus [104].

Recently TAK-721, a budesonide oral suspension (BOS) formulated as an investigational treatment for EoE, was investigated in the US to treat adolescent and adult EoE patients. Initially, 93 patients aged between 11 and 40 years with dysphagia and active esophageal eosinophilia were randomized in a phase 2 trial to receive either BOS 2 mg or placebo twice daily [105]. A greater proportion of patients assigned to BOS achieved histologic remission compared with placebo (39% vs. 3%, respectively), defined as having ≤6 eosinophils per high-power field in all esophageal thirds, after 12 weeks of treatment. Regarding symptoms, a greater drop in the validated DSQ score was demonstrated among patients treated with BOS. Subsequently, a phase 3 trial randomized 2:1 a total of 318 patients aged 11 to 55 years with active EoE to receive a 12-week course with BOS, 2 mg twice daily, or placebo [106]: Overall, 53.1% of patients assigned to BOS therapy achieved histologic remission (≤6 eosinophils/hpf), compared to only 1.0% in the placebo group. Symptomatic improvement (defined as ≥30% reduction in DSQ score) was documented in 52.6% and 39.1% of patients treated with BOS and placebo, respectively.

As for safety, BOS was well tolerated; most adverse events were mild or moderate in severity. In the phase 2 trial there was one case each of esophageal and oral candidiasis in the BOS group; in the phase 3 trial, esophageal and oral candidiasis was documented in 3.8% of patients treated with BOS; only one patient allocated to placebo presented esophageal candidiasis. No differences between groups in cortisol levels, abnormal adrenocorticotropic hormone (ACTH) stimulation test results or growth characteristics (for those aged younger than 18 years) were noted among study groups.

Improvements in endoscopic and histopathological scores were significantly greater among patients allocated to TAK-721 BOS compared to placebo: There was a significantly larger decrease in the BOS group than in the placebo group in total EREFS, and also significant improvements from baseline in EoE-HSS, which are validated scores. However, no data on the potential effect of this budesonide formulation on HRQoL has been provided.

Despite this compound demonstrating some benefit in inducing disease remission and having the potential to be the first treatment for EoE to reach the US market for adolescent and adult patients, the Food and Drug Administration (FDA) recently rejected the approval of the drug and recommended an additional clinical study [107].

The development of viscous formulations for EoE continues with other compounds, and data on the efficacy of a new fluticasone suspension [108] and a viscous mometasone formulation [109] has recently been published.

Available viscous corticosteroid formulations differ in the muco-adhesive capacity of their components. The concentration of the active ingredient and the stability of the product determine esophageal clearance and potentially explain the differences between various available compounds [101]. Any proposal for a standardized formulation of corticosteroid [110] should demonstrate its clinical efficacy.

### 5.2. Orodispersible tablets: an improved approach

In 2018, the European Medicines Agency (EMA) approved a new budesonide orodispersible tablet (BOT) formulation, which is now available in most European countries, as the first drug to induce and maintain remission of EoE in adult patients [111]. A phase 3 RCT that compared BOT 1, mg taken twice daily, with placebo provided an efficacy of over 93% in achieving histological remission (defined by <5 eos/hpf at each esophageal third) after 6 weeks of treatment, with no relevant side effects. In addition, 58% of patients were in complete symptomatic remission under BOT at 6 weeks [112], as measured by a 0–10 numerical rating scale. When therapy length was extended to 12 weeks, this rate increased to 85%. Significant clinical improvement was also demonstrated with the validated EEsAI score.

The ability of this budesonide compound to maintain sustained remission of EoE was subsequently analyzed in another RCT: Patients were randomly allocated to the same dose used to induce remission (1 mg twice daily), half of the dose (0.5 mg twice daily) or placebo [113]. Overall, 73.5% of patients receiving BOT 0.5 mg twice daily and 75% of those receiving BOT 1.0 mg twice daily persisted in clinical and histological remission after 48 weeks of treatment, compared with only 4.4% of patients in the placebo group.

As for safety concerns, histologically confirmed candidiasis was documented in 7.4% and 2.9% of patients treated with BOT 0.5 and 1.0 mg twice daily over 48 weeks, respectively. In addition, no changes in cortisol levels were seen from baseline to the end of treatment.

In addition to providing evidence of efficacy in inducing symptom and histological remission, clinical trials with BOT have examined the ability of this compound to reverse endoscopic findings and its effects on quality of life [112,113]: Short term (6 weeks) treatment with BOT induced significant reductions in total EREFS score from baseline, and also in each of the 5 endoscopic features that integrate it [112]. Extending treatment over 48 weeks further improved patients' endoscopic findings, with fibrosis sub-score improving in both BOT-treated arms. Changes in other endoscopic features were marked among patients assigned to the higher dose [113]. Regarding HRQoL, a treatment length of only 6 weeks demonstrated significant improvements in total scores provided by the EoE-QoL-A disease-specific validated questionnaire, as well as in the five dimensions that integrate the scale [112]. Although patients in the maintenance of remission trial started with a good HRQoL, an additional 10% improvement was demonstrated with active drug at either high or low doses, where deterioration was seen with placebo [113].

Investigation with BOT currently continues with a phase 3 RCT (EudraCT No. 2017–003516-39) which is comparing intermittent or continuous 48-week treatment to placebo, for maintaining clinico-histological remission in adult patients with EoE.

APT-1011 is an effervescent orodispersible fluticasone tablet currently under development for EoE. After demonstrating proof of effectiveness, safety and tolerability in a phase 1b/2a study conducted at seven medical centres in the U.S. [114], the FLUTicasone in EoE (FLUTE) phase 2b trial assessed the best dose regimen to provide an optimal targeting of the esophageal mucosa with the fewest adverse events (EudraCT No. 2016–004749-10). Overall, 103 patients recruited in the U.S. and several European countries were randomly allocated to 4 fluticasone dosages ranging from 1.5 to 6 mg daily, the total daily dose taken either once or twice daily [115]. The 3 mg once daily APT1011 dose was that with the highest benefit/risk ratio (with 80% of patients having ≤6 eosinophils/hpf after 12 weeks of therapy), and it is being now been assessed in the phase 3 trial FLUTE-2 trial (ClinicalTrials.gov Identifier NCT04281108) to induce and maintain EoE remission in adult patients. In addition, the sub-study FLUTEEN trial (NCT05083312) is also being carried out in adolescents. Table 2 summarizes RCT currently being conducted to developed novel STC for EoE on adolescents and adults.

Differences in the effectiveness of the various formulations of budesonide (BOS vs. BOT) could partially rely on how they are dissolved, with the former still requiring a certain volume, while the latter uses the saliva itself secreted by the

Table 2. Novel swallowed topical steroids for eosinophilic esophagitis in adults and adolescents currently being investigated through randomized clinical trials.

| Investigational medicinal product | Target population | Dose comparison | Phase | Study Design |
|---|---|---|---|---|
| BOT (EudraCT 2020–001314-37) | Adults | 1 mg BID vs. 2 mg QD | 3 | DB |
| BOT (EudraCT 2017–003516-39) | Adults and Adolescents | Continuous vs. episodic 0.5 mg BID vs. placebo | 3 | OLI + DB Placebo-controlled |
| APT-1011 (NCT04281108) | Adults and Adolescents | 3 mg HS vs. placebo | 3 | DB + OLE Placebo-controlled |
| APT-1011 (NCT05083312) | Adolescent | 3 mg HS vs. placebo | 3 | DB Placebo-controlled |
| ESO-101 (NCT04849390) | Adults | 800 mcg vs. placebo | 2 | DB Placebo-controlled |

APT-1011, fluticasone propionate orally disintegrating formulation; BID, twice daily; BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; DB, double-blind; ESO-101, mometasone furoate hard gelatin capsule; EudraCT, EudraCT number; HS, at bedtime; NCT, Clinicaltrials.gov identifier; OL, open-label induction; OLE, open-label extension; QD, once daily.

effervescent stimulus of the tablet. Bearing in mind that the esophagus is a muscular organ with the function of quickly conducting boluses to the stomach and that its capacity is only virtual, a smaller volume of solution (the secreted saliva itself) could represent an additional advance therefore.

### 5.3. Adhering the medication to the esophagus: the last frontier?

Recently, a system consisting of a rolled muco-adhesive polymer film contained into a hard gelatin capsule, which unfolds along the esophagus after been swallowed, has been developed. The so-called EsoCap system, is proposed as a novel drug delivery device that enables targeted placement of medication on the esophageal mucosa [116]. The first clinical application of EsoCap is a phase 2 RCT to investigate the safety, tolerability, and effectiveness of this technology, containing mometasone 800 µg and applied once daily compared to placebo, to induce disease remission in adult patients with active EoE (NCT04849390). However, EsoCap system may potentially treat different esophageal diseases.

## 6. Investigational therapies for EoE: a glimpse towards molecular and personalized medicine

Over the last decade, the genetic and molecular bases of EoE have started to be revealed [23,24]. Although not fully understood, the role of different molecules (including cytokines, chemokines, and their signaling pathways) in inducing changes in epithelial permeability, recruitment of eosinophils to the esophagus, and their subsequent activation, have made it possible to evaluate the effectiveness of several new targeted therapies, many of which have been previously investigated in the treatment of bronchial asthma and atopic dermatitis. Late-phase clinical trials are currently investigating monoclonal antibodies (mAbs) against various cytokines and Siglec-8 blockers, after providing some preliminary proof of the potential of these drugs to control not only esophageal symptoms and eosinophilic inflammation in patients with EoE, but also some concomitant atopic manifestations that these commonly present [117]. These new developments have recently been described in detail elsewhere [117,118], so they will only be briefly addressed in this paper.

These new therapies could be beneficial for a proportion of patients who do not yet have an adequate treatment option. But at the same time, its intense development in recent years reflects the great interest aroused by pharmaceutical companies in the expanding market offered by the growing epidemiology of EoE. The main investigational therapies to treat EoE in adults are summarized in Table 3.

### 6.1. Monoclonal antibodies to targeting Th2 type inflammation in EoE

As in EoE, in eosinophilic asthma, eosinophils increase in the peripheral circulation and accumulate in the airway wall and lumen, causing mucus hypersecretion, bronchoconstriction, and airway remodeling [119]. Three different strategies are currently being investigated in EoE aimed at blocking the effect of Th2 cytokines: depleting eosinophilic infiltration through blocking the IL-5 signaling pathway, blocking IL-13-mediated biological effects, and the most successful IL-4 blockade.

The IL-5 blockers mepolizumab and reslizumab were tested a decade ago in patients of all ages with EoE: Both drugs were able to reduce blood and esophageal eosinophilia, but all patients maintained a peak eosinophil count over 20 eos/hpf in esophageal mucosal biopsies; as symptoms did not changed significantly, further studies with these drugs in EoE were abandoned. Recently, benralizumab, a new mAb directed against the α chain of the IL-5 receptor (IL5RA), has revitalized interest in this mechanism, and a currently ongoing phase 3 RCT is comparing the effectiveness of benralizumab over placebo to reduce histopathology and symptoms in adolescents and adults with EoE (NCT04543409).

A pivotal role has been recognized to IL-13 in EoE, as this Th2 cytokine promotes epithelial dysfunction with increased permeability, fibrous remodeling and production of the eosinophil chemoattractant eotaxin-3[23]. After the insufficient effectivenss provided by dectrekumab (the first anti-IL-13 mAb tested in EoE) Cendakimab is now being investigated in this disease: Some effectiveness compared to placebo were demonstrated in a phase 2 RCT [120] which tested two weekly subcutaneous (SC) injectable doses: 50% of patients treated with either active drug dose had <15 peak eos/hpf after a 16-week therapy. EREFS score was reduced over placebo in patients treated with cendakimab, despite almost no patients achieved esophageal normalization.

Table 3. Potential novel treatment options for eosinophilic esophagitis under current investigation.

| Investigational medicinal product | Target population | Phase | Study design | Mechanism of action |
|---|---|---|---|---|
| Benralizumab (NCT04543409) | Adults and adolescents | 3 | DB+OLE Placebo-controlled RCT | IL-5 receptor α monoclonal antibody, SC injection |
| Cendakimab (NCT04753697) | Adults and adolescents | 3 | DB Placebo-controlled RCT | IL-13 monoclonal antibody, SC injection |
| Cendakimab (NCT04991935) | Adults and adolescents | 3 | OLE | IL-13 monoclonal antibody, SC injection |
| Dupilumab (NCT03633617) | Adults and adolescents | 3 | DB+OLE Placebo-controlled RCT | IL-4 receptor α monoclonal antibody (blocks IL-4 and IL-13), SC injection |
| AK002 (NCT04322708) | Adults and adolescents | 2/3 | DB+OLE Placebo-controlled RCT | Siglec-8 monoclonal antibody, IV infusion |
| APD334 (NCT04682639) | Adults | 2 | DB+OLE Placebo-controlled RCT | S1PR1 modulator, oral tablet |

AK002, lirentelimab; APD334, etrasimod; DB, double-blind; IL, interleukin; IV, intravenous; NCT, Clinicaltrials.gov identifier; OLE, open-label extension; RCT, randomized clinical trial; SC, subcutaneous; Siglec-8, sialic acid-binding immunoglobulin-type lectin 8; S1PR1, sphingosine-1-phosphate receptor 1.

However, clinical benefit was not superior to that obtained with placebo. Currently, a phase 3 RCTs is being conducted with cendakimab at 360 mg dose compared to placebo in adult and adolescent patients with active EoE (NCT04753697), with no results from this trial available to date.

Finally, the modest results provided by IL-13 mAbs in several Th2 diseases, motivated the development of the IL-4 blocker dupilumab. As both IL-4 and IL-13 bind to a common receptor complex (IL-4Rα and IL-13Rα1) and exert overlapping biological effects [121], blocking IL-4 with dupilumab could provide greater effects by inhibiting the signaling of the IL-4 and IL-13 proteins. Dupilumab, which is currently approved by the FDA and EMA for the treatment of moderate-to-severe atopic dermatitis, severe asthma, and chronic rhinosinusitis with nasal polyposis, has also provided evidence of effectiveness in active EoE [122] and appears as a promising therapy according to results of an still ongoing phase 3 RCT [123]. According to it, 59.5% of patients treated with SC injections dupilumab 300 mg weekly presented ≤6 eosinophils/hpf at week 24, compared to only 5.1% of the patients who received placebo. In addition, dupilumab induced significantly greater symptomatic improvement than placebo on the DSQ. This benefit was observed as early as at the fourth week of treatment, and persisted over the complete 24-week duration of the trial [123].

### 6.2. Anti-siglec-8 antibodies to promote apoptosis of eosinophils

Sialic acid-binding immunoglobulin-type lectins (or Siglecs) are cell surface proteins that bind sialic acid. There are 14 different mammalian Siglecs, which are found primarily on the surface of different immune cells, including eosinophils and mast cells. These cells mostly express the inhibitory receptor Siglec-8[124], which participates in apoptosis and elimination of eosinophils, in inhibiting the release of mediators by mast cells and the reversal of tissue remodeling. The anti-Siglec-8 mAb lirentelimab (AK002) recently demonstrated effectiveness in improving tissue eosinophilia and symptoms in patients with eosinophilic gastritis and duodenitis in a phase 2 RCT [125], and patients who had esophageal involvement also showed reductions in esophageal eosinophil counts and less difficulty swallowing. Currently, a phase 2/3 study (NCT04322708) is being carried out in patients with active EoE.

### 6.3. Targeting lymphocytes instead of eosinophils: sphingosine-1-phosphate agonists for EoE

Sphingosine-1-phosphate (S1P), a signaling sphingolipid, acts as a bioactive lipid mediator by signaling through the five different cell surface receptors named S1PR1 toS1PR5, each of which generates different biological effects.

S1P is recognized as a major regulator of trafficking of T- and B-cells: After interacting with its receptor S1PR1, S1P egresses immune cells from the lymphoid organs into the lymphatic vessels [126]. Therefore, S1PR modulators are able to treat several immune-mediated diseases [127], including EoE. Etrasimod (APD334), a selective ligand of S1P1R1, S1PR4, and S1PR5 is currently being studied in EoE in a phase 2 RCT (NCT04682639).

As with other Th2 cytokine blockers, the advantages of oral administration of S1PR modulators and their potential effectiveness on different immunoallergic-based diseases, which frequently occur in the same patient would consist of controlling several diseases with a single drug.

## 7. Conclusion

Advances in the pharmacological treatment of EoE have been remarkable in recent years. Once the position of PPIs in the patient care algorithm had been clarified, these drugs now constitute an effective and convenient alternative for a proportion of patients. New standardized formulas of STC with better mucoadhesive capacity allow increased esophageal exposure time to the drug and reduce its esophageal clearance, thus providing improved effectiveness at lower doses. Patients who do not respond or are intolerant to the above will soon be able to benefit from new drugs in an advanced stage of development, which are aimed at

controlling different inflammatory cascades common to other Th2-mediated diseases.

## 8. Expert opinion

The pharmacological treatment of EoE, more than any other aspect of the disease, has seen the greatest change most recently. This has been mainly due to three reasons: (a) The definition of the role of PPIs as a true therapy for EoE and not as a diagnostic instrument; (b) The development of novel formulations of topical corticosteroids for a standardized treatment of patients, which ensure an effective release of the drug in the esophagus and allow predictable effectiveness, and (c) The interest that EoE and its expanding epidemiology has aroused in the pharmaceutical industry. The latter is currently developing multiple targeted therapies, with the potential to advance individualized therapy and overcome the limitations of previous treatments. Each of these aspects, however, deserves a critical analysis.

PPIs are an accessible, widely available, cheap, and cost-effective therapy for the treatment of EoE. Despite this, they are one of the least effective options demonstrated: Even with double daily doses, only half of the patients achieve histological remission of EoE (defined as an eosinophil density in esophageal biopsies below the diagnostic threshold of 15 cells per hpf) and only 1 in 3 achieve deep remission of the inflammation. Where there is success, one in four patients is not able to reduce to standard doses to maintain long-term remission. There is currently a lack of non- or minimally invasive markers to monitor response to treatment in EoE [128], so patients must undergo endoscopies with repeated biopsies to determine response to therapy. Despite limitations, PPIs are the most widely used first-line treatment option globally for EoE, and are only inadvisable for patients with very severe symptoms and a marked deterioration in their HRQoL (for those whom ensuring a highly effective therapy as soon as possible is critical), and in those with esophageal strictures or narrow-caliber esophagi, (where this therapy has been shown to be less effective).

The accumulated experience with swallowed corticosteroids has shown that topical treatment of the esophagus represents a real challenge, due to the anatomical and functional characteristics of the organ. To begin with, it is tubular, usually placed vertically (thus favoring the effect of gravity), and with a distal outlet to the stomach. Liquids and solids from the diet repeatedly pass through it, preventing material being retained there. In case of fasting, saliva is also effective in washing the internal esophageal surface. Finally, the esophagus is subject to peristaltic dynamics, which, although they may be altered in active EoE [129,130], will ensure clearance of the organ as soon as the inflammation resolves. Lack of a homogeneously developed viscous formula to release corticosteroids in the esophagus has resulted in widely variable effectiveness and a high rate of non-responder patients. Commercially developed viscous formulas of budesonide also have limitations, and orodispersible tablet preparations may currently be the best option for topical treatment of EoE. A recent network meta-analysis comparing all available RCTs on EoE drugs showed BOT as the most effective therapy to induce remission [131]. Cost-utility analysis reinforce this data [132], so future developments should only be considered potentially useful if they exceed the effectiveness of BOT.

However, efficacy is not the only problem associated with corticosteroid formulations used to treat EoE. As in other chronic diseases, once free of symptoms, adherence to EoE treatment is a problem in real life, and long-term remission rates have been reported to be quite low, leading to high relapse rates regardless of the regimen used (high or low corticosteroid dose) [133,134]. This problem could be especially relevant in adolescent patients [135], so strategies aimed at improving adherence (including simpler once-daily dosing schedules, or mobile phone reminder tools for patients [136]) could be advisable.

New biological drugs and oral immunomodulatory molecules under development undoubtedly represent an opportunity for patients who do not respond to other current alternatives (although this proportion is minimal when appropriate corticosteroids-based formulas are used); or when they present intolerable toxic effects (such as repeat oropharyngeal or esophageal candidiasis). None have shown the ability to modify the natural history of EoE so far, and their long-term safety and effectiveness have yet to be established. Biologic therapy has been related with an increased risk of immune-mediated effects, including cross-reactivity, reactions derived from immune imbalance, over-stimulation, and hypersensitivity reactions [137]. Likewise, the generation of neutralizing antibodies may lead to loss of response, which could be recovered by using higher mAb doses, shorter administration intervals and by associating immunosuppressant drugs [138] (as documented in other immune-mediated diseases). The most realistic scenario for the use of these new drugs in development, if approved, would be for the treatment of a patient with several concomitant conditions of a certain severity that can be treated with a single drug. The cost and future cost-effectiveness studies will largely determine the line of treatment in which they can be positioned.

Finally, the recent proposal of homogeneous therapeutic objectives for the new drugs under development for EoE [69] will allow direct comparisons among different therapies available or under development. It will also generate greater knowledge to position the different treatment options based on objective criteria, effectiveness in reducing symptoms, inflammation and the impact of the disease on EoE patients and their families.

## Abbreviations

ACTH: adrenocorticotropic hormone; BOS: budesonide oral suspensión; CI: Confidence interval; DSQ: Dysphagia Symptom Questionnaire; EEsAI: Eosinophilic Esophagitis Activity Index; EMA: European Medicines Agency; EoE: eosinophilic esophagitis; EndoFLIP: endoscopic functional lumen image probe; EREFS: Edema, Rings, Exudates, Furrows, Stricture; FDA: Food and Drug Administration; GERD: gastroesophageal reflux disease; hpf: high-power field; HRQoL: Health-related quality of life; HSS: EoE Histology Scoring System; IL: interleukin; mAb: monoclonal antibody; P-CAB: Potassium-competitive acid blockers; PEESS: Pediatric EoE Symptom Score; PPI: proton pump inhibitors; PPI-REE: Proton pump inhibitor-responsive

esophageal eosinophilia; PRO: patient reported outcomes; RCT: randomized controlled trial; STC: swallowed topic corticosteroids; S1P: Sphingosine-1-phosphate; S1PR: Sphingosine-1-phosphate receptor; Th2: T helper 2; TSLP: thymic stromal lymphopoietin; US: United States

## Declaration of Interest

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•• **A consensus conference sough to develop a harmonized core outcome set (COS) of end points to be used to determine treatment efficacy in eosinophilic esophagitis (EoE). Using common outcomes measures in observational studies and controlled studies with pharmacologic and dietary interventions in patients of all ages with EoE will facilitate evidence synthesis and appraisal when comparing different treatments**
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