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REVIEW



# Current options and investigational drugs for the treatment of eosinophilic esophagitis

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**ABSTRACT**

**Introduction:** Current treatments of eosinophilic esophagitis (EoE) induce symptomatic and histological remission in a proportion of patients. However, they do not fully meet patients' needs and limitations should be acknowledged. The growing epidemiology of EoE has generated a great interest for research into novel therapeutic approaches.

**Areas covered:** This article discusses current therapies available for EoE, those under investigation and presents potential additional ones. Established anti-inflammatory treatments for EoE include dietary therapy, proton pump inhibitors, and swallowed topical corticosteroids, which are combined with endoscopic dilation in cases of strictures. Refractoriness, recurrence after treatment-cessation, and need for long-term therapies have encouraged investigation of novel, esophageal-targeted formulas of topical corticosteroids and of new therapeutic approaches directed at blocking the molecular pathways that lead to inflammation in EoE. These include monoclonal antibodies (including mepolizumab, reslizumab, benralizumab, dectrekumab, cendakimab, and dupilumab), JAK-STAT blockers, and S1PR agonists, among others. Some have provided evidence of effectiveness and safeness in the short-term use.

**Expert opinion:** Therapies under investigation potentially can target multiple Th2-associated diseases that converge in EoE patients. Therapeutic strategies require a personalized and patient-centered approach to reduce the burden of the disease, and cost-effectiveness analysis to position their use in a complex therapeutic landscape.

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Eosinophilic esophagitis (EoE); swallowed topical corticosteroids; budesonide; fluticasone; food-elimination diet; proton pump inhibitor (PPI); biological therapy; mepolizumab; reslizumab; benralizumab; cendakimab; dupilumab; etrasimod

## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, antigen-driven inflammatory disease, histologically characterized by dense esophageal eosinophilic infiltration and typically presenting with symptoms related to esophageal dysfunction [1,2]. Once considered a rare condition, there has been a dramatic rise in the recognition of EoE during the last decade, especially in Western countries [3]. EoE currently affects at least one in 2,000 people in Europe and the US [2] and today is recognized as the most prevalent cause of dysphagia and food impaction in children and young adults, and as the second cause of chronic esophagitis, after gastroesophageal reflux disease (GERD) [4]. Left untreated, inflammation and symptoms tend to persist over time [5] and grow more intense, as the disease leads to esophageal remodeling with stricture formation and functional damage [6–8]. The progressive nature of the disease, together with its recurrent symptoms, such as feeding difficulty, pain, and vomiting or dysphagia, has an important impact on patients' health-related quality of life (HRQoL) [9], and this clearly indicates the need to treat symptomatic patients.

Being a unique form of non-IgE-mediated food allergy triggered mainly by food antigens [10], strategies based on the elimination of food triggers have been shown to be the only therapy that targets the cause of EoE, inducing and maintaining its remission [11]. There are no current food allergy tests that accurately predict food triggers for EoE [12], so empirical elimination of foods more commonly involved in triggering food allergy achieves the most consistent results [13]. Swallowed topic corticosteroids (STC) have been shown to be effective in inducing histological remission of the disease [14–16], and novel formulations targeted at coating the esophageal mucosa also provide symptomatic relief [17–19]. Proton pump inhibitors (PPIs) are an effective first-line therapy [20] able to achieve [21] and maintain [22–24] histological and symptomatic remission in a half of patients. This is due to their anti-inflammatory effect, independent of their action on gastric acid secretion [25,26]. Finally, up to 95% of patients have shown symptom relief following esophageal dilation [27]. This should be considered in patients with fibrostenotic esophageal complications and persistent dysphagia/food impaction, despite them being under an effective anti-inflammatory treatment [28].

EoE was first characterized in the early 1990s as a distinct clinical entity, different from eosinophilic gastroenteritis [29,30]. Since then there has been an emergence of research

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**Article highlights**

- The therapeutic goals in EoE include achieving clinical-histological and endoscopic remission, the prevention of remodelling-related complications and nutritional deficiencies, correcting eating/feeding dysfunction, and maintaining an adequate health-related quality of life.
- Current available therapies that have shown to achieve and maintain remission in EoE include diet, PPIs and swallowed topical corticosteroids. These can be combined with endoscopic dilation in cases of fibrostenotic complications. Any of these therapies needs to be used for the long term, as symptoms recurrence is usual after treatment cessation.
- The better understanding of the pathogenesis of EoE has allowed to identify new potential therapeutic targets.
- Considering that EoE is a Th2-mediated disease, monoclonal antibodies targeting interleukin (IL)-4, IL-13 and the α subunit of the IL-5 receptor (IL-5Rα), used for other Th2-mediated allergic diseases, are being investigated for EoE in late-phase clinical trial.
- Siglec-8 blockers able to induce eosinophil apoptosis, and etrasimod, an S1PR agonist, are also promising therapies to be incorporated into clinical practice.
- The treatment strategy needs to be individually agreed with the patient through a shared decision-making model, aiming to ensure adequate long-term monitoring and to meet patient's needs.

This box summarizes key points contained in the article.

on its causes and treatment[31], however potential risk factors and the ideal therapy for EoE remain undefined. Over the last decade, several consensus documents and practice guidelines have provided a structured and evidence-based framework for treating patients with EoE [1,32–34]. However, many patients' needs are still unmet, and significant variations in adherence to guidelines regarding treatment choice and assessment of response have been documented [35–38]. These limit the evaluation of the effectiveness of the available therapies for EoE and prevent the optimization of its clinical management [39].

The aim of this article is to summarize the goals and effectiveness of current pharmacological options for treating EoE, as well as to discuss limitations of the available treatment approaches. Novel alternatives, potential therapeutic targets under current investigation, and others on the horizon are also discussed.

## 2. Therapeutic goals in EoE and limitations when assessing effectiveness

Since the identification of the disease the therapeutic targets for EoE have evolved from mere symptomatic improvement to, ideally, complete resolution of symptoms, histological and endoscopic remission (mucosal healing), and prevention of remodeling and related complications [40,41] such as fibrotic strictures. Current treatment endpoints should also include improving patients' HRQoL, restoring social activities [42,43], correcting feeding dysfunction, and preventing nutritional deficiencies, especially in children [2]. A further target to be achieved is avoiding drug side effects and long-term diets [44]. An interdisciplinary Delphi process has recently proposed that core outcomes set for controlled studies of pharmacological and diet interventions in patients with EoE of all ages should consists of four pivotal outcomes: patient-reported symptoms, histopathology, endoscopy, and EoE-specific HRQoL [41].

Evaluating these goals is, however, complicated, since a major challenge in EoE therapy is the lack of validated definitions for symptomatic, endoscopic, and histological remission. There is also evident heterogeneity in the reporting of outcomes due to the use of varying and unvalidated instruments, and variable study methodology [31]. When assessing symptomatic resolution, it needs to be taken into account that patients with EoE frequently show poor correlation between symptoms and eosinophil density in esophageal biopsies [45,46]. In fact, improvement or lack of symptoms does not always correlate with changes in disease activity or remission, as patients often develop adapting behaviors to cope with swallowing difficulties [47], purposely or subconsciously, which in turn can potentially lead to a change of their perception of the disease and how it affects their daily routine. Examples of these adaptations are: prolonged eating time, modification of food texture, avoiding highly solid food, or restricting social activities. Often these behaviors are not reflected in routine clinical assessments, nor are they captured by generic instruments used to assess dysphagia [48,49]. Younger patients may find difficulty in fully describing their symptoms, which can be different from those for adolescents and adults [50,51]. Disease-specific instruments have been developed to capture all these characteristics and to be used in clinical trials [52–54]. Unfortunately, these instruments have not yet been applied in real-world practice [55].

Assessment of histological remission also presents a challenge, as the specific threshold for reduction in peak eosinophil count to determine treatment efficacy remains undefined, having been established at variable degrees during the trials. In regular clinical practice, a peak eosinophil count below 15 eosinophils per high power field (eos/hpf) is appropriate to identify histological response for patients with symptoms and endoscopic improvement [56]. However, most clinical trials are defining a histological threshold lower than 6 eos/hpf, which is also being suggested by the Food and Drugs Administration [57]. Although histological evaluation is currently focused on eosinophilic infiltration, other histological findings should be taken into consideration. An EoE histology scoring system (HSS) [58] has being developed and validated to grade eight pathological features in esophageal biopsies and provides additional support to define EoE remission and differential diagnosis from other conditions [41,59]. This EoE HSS provides an objective assessment of histological esophageal changes in addition to just eosinophils count alone [60], and its potential advantages are being evaluated by a number of randomized clinical trials (RCT) [61].

Currently, endoscopic improvement is emerging as a relevant therapeutic goal in clinical trials, which would complement the two primary endpoints (i.e. symptom resolution and histological remission) [49]. Endoscopic improvement can be assessed with the EoE Endoscopic Reference Score, which grades the five major esophageal features of EoE: Edema, Rings, Exudates, Furrows, and Strictures (EREFS)

[62]. Endoscopic healing, especially with regard to fibrotic features, is now included as an important target for any EoE treatment, despite an endoscopic remission criterion still needing to be agreed [63]. In the future, novel parameters of esophageal distensibility [64] and biomarkers of eosinophil activity or gene expression panels [65] may also be included as treatment outcomes.

## 3. Current therapeutic options for EoE: effectiveness and limitations

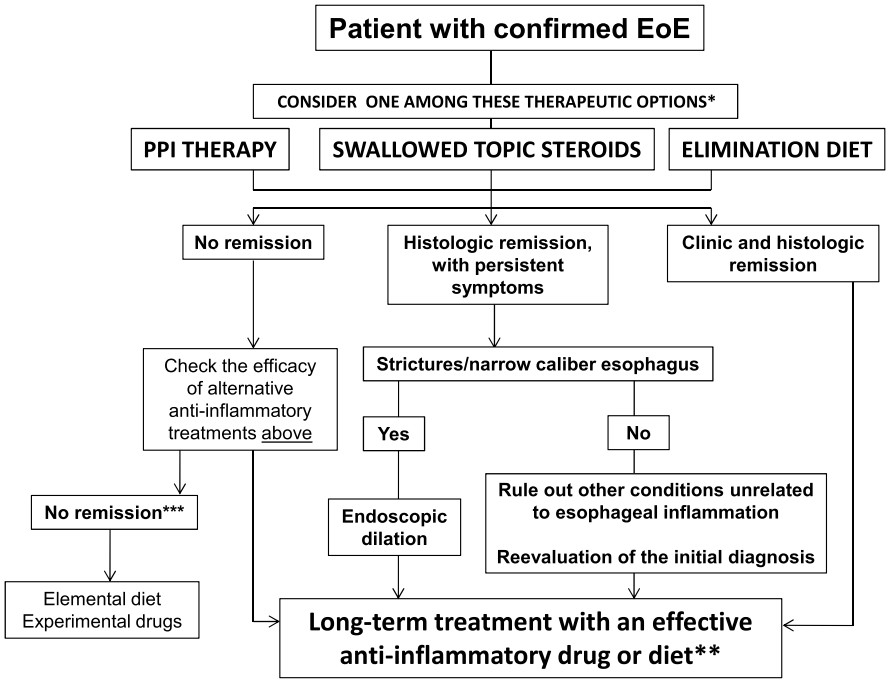
Currently, first-line anti-inflammatory therapies offered for EoE patients include dietary modifications, PPIs, and STC, which are combined with esophageal dilation if esophageal strictures or narrow-caliber esophagi are noted. Figure 1 summarizes the proposed therapeutic approach algorithm for EoE[1]. The choice of treatment should initially be agreed with the patient and could change over time. A follow-up endoscopy should be performed to assess the efficacy of any therapy 6 to 12 weeks after the initial course. Effective therapies that induce EoE remission are usually continued to maintain remission; lack of response requires an alternative first-line option assessment. Despite this, a change of therapy might be necessary in the long-term due to treatment side effects, unwillingness of the patient to continue with a diet or medication, or when a negative impact on patient's quality of life or family resources is produced [1].

### 3.1. Dietary therapy

Dietary therapy in EoE includes either an elemental, allergy testing-directed food restriction or empirical food elimination approach. Elemental diets involve the ingestion of only an amino acid-based, allergen-free elemental formula, which, due to its many disadvantages, in real practice is limited to young children and for a short period of time [11]. Currently, there is no allergy test available able to correctly identify food trigger(s) of EoE [12], so empirical food elimination remains the only feasible approach to patients willing to try dietary therapy. Avoiding the six most common food allergy triggers (i.e. dairy, soy, peanuts, wheat, egg, and seafood) for a period of 6 weeks has repeatedly induced remission in about 3/4 of patients [66,67]. Sequential food reintroduction identifies specific food triggers by demonstrating histological disease recurrence. Novel approaches, including the elimination of only 4 [68,69] or 2 foods [70], minimize dietary restriction and endoscopy burden, and identifies early on patients who respond poorly to dietary therapy. Long-term compliance with a severely restricted diet has been shown to be low [71–73], which, together with the burden of multiple endoscopies required to verify disease remission and to evaluate recurrence after food challenges, restricts this treatment option to the most motivated patients.

### 3.2. Proton pump inhibitors

The role of PPIs in EoE has evolved from initially being used as an instrument to rule out GERD as a cause of esophageal




*In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered
** After response to any empiric 6-week diet, all food groups should be reintroduced individually, with an endoscopy performed following each food challenge. The final goal is a long-term removal solely of foods proven to induce EoE
*** Refer the patient to an EoE center

Figure 1. United European Gastroenterology recommended therapeutic algorithm for treatment of eosinophilic esophagitis. This figure has been reproduced with permission from Lucendo AJ, Molina-Infante J, Arias A, 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: 335–358.

eosinophilia [32], to a differential diagnostic tool of a provisional clinical entity (the so-called PPI-responsive esophageal eosinophilia) [33] to finally being identified as a first-line anti-inflammatory treatment for EoE [1]. From the early pediatric literature [74–76], off-label use of PPIs in EoE provided evidence of the potential to achieve both clinical and histological remission of EoE, with anti-inflammatory properties that are independent from effects on acid secretion, and which were first shown in EoE. PPI therapy substantially downregulated esophageal gene expression of eotaxin-3/CCL26 and T helper (Th)-2 cytokines interleukin (IL)-5 and IL-13 in biopsies from patients with EoE, and similarly in patients treated with topical steroids [77]. It also restored the esophageal transcriptome characterizing EoE in esophageal biopsies similar to STC [78]. A systematic review of 33 studies (11 prospective) demonstrated double-dose PPI therapy was able to induce histological remission of EoE (defined as a reduction of eosinophilic infiltrate below 15 eos/hpf) in 50.5% of patients (95% CI, 42.2–58.7%) and any symptomatic improvement in 60.8% (95% CI, 48.38–72.2%) of treated patients [21]. More recently, a Technical Review from the AGA Institute reproduced the aforementioned effectiveness in terms of histologic disease remission after summarizing in a meta-analysis the results of 23 studies [67]. A wide inconsistency in the results of the different studies was noted, as doses, treatment lengths and PPI drugs used varied among them. Among responders, the long-term strategy is to use the minimal effective dose to maintain remission. Standard PPI doses effectively maintained clinico-histological remission in 69.9% of initial responders [26]. Despite this therapy generally being considered safe, recent concerns have arisen around the potential complications with long-term use of PPI [79,80]. However, potential adverse effects of PPIs are likely overestimated by the presence of confounding factors in most studies, generating an unnecessary controversy about the safety of PPIs [81].

### 3.3. Topic corticosteroids

Topically administered corticosteroids with reduced bioavailability, swallowed instead of inhaled, have been used as a first-line therapy from the initial descriptions of EoE. A small series of four children proved that STC were as effective as systemic corticosteroids in inducing clinical and histological remission [82], and provided similar advantages in terms of symptom resolution, recurrence rates and time to relapse. As the former had significantly less side effects, they now constitute a common therapy for EoE, while systemic corticosteroids are exclusively restricted to emergency situations of severe dysphagia or significant weight loss.

To treat EoE, off-label preparations of topic corticosteroids, marketed for asthma or rhinitis and in the form of metered dose inhalers, nasal drops, or nebulizer solutions, should be swallowed instead of inhaled [67]. Although both fluticasone and budesonide have shown comparable potencies, the method used to deliver the topical steroid over the esophageal mucosa is as important as the drug itself. In fact, a RCT demonstrated that, when compared to nebulized budesonide at the same dose, oral viscous budesonide provided a higher level of esophageal coverage and a more prolonged contact between the mucosa and the medication, thus leading to a greater reduction of esophageal eosinophil counts and endoscopic normalization [83].

A new budesonide orodispersible tablet (BOT) formulation was approved by the European Medicines Agency in 2018 as the first drug to treat EoE in adult patients, and it is now available in most European countries [84]. This BOT formulation provided an efficacy over 93% in achieving histological remission after 2 to 6 weeks of treatment, without significant side effects. Regarding symptomatic remission, at 6 weeks, 58% of patients given BOT were in complete remission compared with no patient who received placebo. This proportion increased to 85% when treatment length was extended to 12 weeks. However, its use in USA and other continents has not been authorized yet. Dose ranges and specific instructions to administer STC in EoE are summarized in Table 1.

In recent years, several systematic reviews with meta-analyses have summarized evidence from a number of RCTs demonstrating the efficacy of STC in inducing remission of EoE [14,16,85]. Both budesonide and fluticasone propionate were shown to be superior to placebo in reducing eosinophilic

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

| Drug | Target population | Induction dosing (usually divided doses) | Maintenance dosing (usually divided doses) |
|---|---|---|---|
| Fluticasone propionate[a,b] | Children | 880–1760 µg/day | 440–880 µg/day |
| | Adults | 1760 µg/day | 880–1760 µg/day |
| Fluticasone propionate suspension[c] | Adults | 2000–4000 µg/day | not reported |
| Budesonide viscous solution[d] | Children[e] | 1–2 mg/day | 1 mg/day |
| | Adults | 2–4 mg/day | 2 mg/day |
| Budesonide orodispersible tablet[f] | Adults | 2 mg/day | 1 mg/day |
| Mometasone furoate | Adults | 800 µg/day[g] | not reported |
| Mometasone viscous suspension[h] | Children | 750 to 1500 µg/day, depending on patient's height | not reported |
| Beclomethasone dipropionate[i] | Adults | 320 µg/day | not reported |

[a]If an inhaler is used, the patient 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]Specific doses in children will be determined by age, height, or weight.
[f]Available in several European countries, the daily dose is divided into two doses.
[g]Four doses of 50 micrograms applied orally by spray 4 times daily
[h]A 150 mg/mL suspension is composed of powder forms of mometasone furoate, hydroxypropyl methylcellulose, potassium sorbate, citric acid, stevia, sodium benzoate, and liquid flavoring agent.
[i]Provided at inhalation aerosol 80 µg per puff, 2 puffs swallowed twice a day

infiltrate below 15 eos/hpf (OR 24.6; 95% CI 7, 86.8) [15] and in achieving complete histological remission (OR 14.8; 95% CI 3.2, 69.2) [16]. Recently, one systematic review showed budesonide to be significantly superior to placebo in terms of symptomatic relief (OR 7.20; 95% CI 2.15, 24.05), but not fluticasone propionate (OR 1.27; 95% CI 0.44, 3.65) [16]. To explain these differences, it needs to be taken into account the several doses assessed in the different studies, the different drug administration methods used to deliver topic steroids inside the esophageal lumen and the use of non-validated instruments for symptoms assessment in older trials.

On STC, clinical and histological remission is usually achieved after 6 to 12 weeks of treatment, but drug discontinuation leads to symptomatic and histological relapse as they do not modify the natural history of the disease [86]. Evidence on the long-term effectiveness of maintenance doses of STC has started to be provided: one-year maintenance of remission therapy with BOT demonstrated that clinic-histological remission was maintained in 74.3% of patients treated with budesonide, but only in 4.4% of patients treated with placebo, with no significant difference found for 1 mg BID or 0.5 mg BID budesonide doses [87]. Such data supports the recommendation of continuing treatment with STC in order to maintain remission in those initially steroid-responsive patients.

As per the safety profile, esophageal candidiasis represented the most common side effect of STC, described in up to 10% of patients of all ages. Most cases were asymptomatic incidental findings during scheduled endoscopies that were resolved successfully after specific treatment, and with no need to withdraw steroid therapy. Used in the long term, topical corticosteroids did not increase rates of candidiasis [87]. There have been no reports of clinical signs of adrenal insufficiency or growth impairment in children so far [88], but current advice is to monitor cortisol levels in children with EoE, especially if high doses for prolonged periods are needed, or if inhaled/nasal corticosteroids are also used to treat concomitant atopies [1].

### 3.4. Antiallergic drugs are not effective for EoE

Despite EoE is recognized as an allergic disease that shares many common physiological and clinical aspects with other Th2-type atopic diseases, antiallergic drugs have provided disappointing results. Thus, the mast cell stabilizer cromolyn, which is effective to prevent the release of histamine and other inflammatory mediators and to decrease activated eosinophils in the bronchial mucosa of asthmatic patients [89], provided no benefit on symptoms or inflammation in children with EoE in early case reports [90]. Later on, a RCT investigated the effectiveness of viscous cromolyn for EoE in 16 children, who showed no changes in esophageal or blood eosinophilia after 8-week treatment, with no significant benefit over symptoms compared to placebo being noted [91].

The leukotriene D4 receptor blocker Montelukast inhibits mast cell degranulation in the bronchial mucosa, the skin and the gastrointestinal tract mucosa, thus being effective as maintenance treatment in several Th2-type allergic diseases [92,93]. However, montelukast used at standard doses was not able to induce histologic response in an open-label trial in children with EoE [94]. In adults, Montelukast was not superior to placebo to maintain EoE in remission [95,96].

### 3.5. Unresolved aspects of current therapies for EoE

Unresolved aspects of the current therapy approaches include: long-term difficulties to maintain adherence to restrictive diets [12,71,72]; the limited effectiveness of PPIs and the need for double doses to maintain remission in a proportion of patients [26]; the reduced effectiveness of STC formulas not developed to target the esophageal mucosa, which could require high doses and pose potential risks; and the need to maintain a daily and long-term therapy. Eventually, inflammation and symptoms recur after discontinuation of any therapy, and to date no therapy has demonstrated the ability to modify the natural history of EoE. Minimal effective maintenance drug doses have not yet been defined for EoE, and no agreement exists as to the methods and frequency of patient assessment and follow-up.

New drugs and formulation of already available options are currently being developed to respond to the still unmet needs of a significant proportion of patients with EoE, who obtain no benefit from available therapies [97]. As a result, a major change in current EoE treatment regimens is anticipated in the near future.

## 4. Potassium-competitive acid blockers: a potential new therapy beyond PPI

First developed in the 1980s, potassium-competitive acid blockers (P-CAB) have recently emerged as a new class of antisecretory drugs characterized by a better pharmacological profile than PPIs. Its rapid onset of action, longer lasting acid suppression, better control of nocturnal acidity and reversible inhibition of the proton pump ($H^+$,$K^+$-ATPase α subunit), has the potential to overcome unmet needs of a proportion of patients who still experience symptoms or mucosal lesion despite PPI treatment [98,99]. Evidence suggests vonoprazan fumarate (the best studied drug in this class) can be preferred to PPIs as maintenance therapy for reflux esophagitis and eradication of *Helicobacter pylori* owing to its stronger antisecretory effect, with a favorable safety and tolerability profiles. Emerging evidence also shows that vonoprazan is effective in patients with EoE. Used at standard doses, vonoprazan showed similar efficacy to PPIs in a large series of 118 Japanese patients [100]. Other reports, however, have shown that vonoprazan was superior to PPI, as up to two-thirds of nonresponsive EoE patients initially treated with a PPI achieved disease remission [101,102]. At present, vonoprazan is exclusively marketed in Japan, and rebaprazan has been approved to be used in South Korea. More research should be done to assess P-CAB efficacy in Western populations and their safety in patients treated in the long term.

## 5. Novel topical corticosteroid formulations on the horizon

New treatment regimens and formulations of STC are currently under investigation. To begin with, a budesonide oral

suspension (BOS) is being investigated in RCTs involving adolescent and adult patients in the US: in a phase 2 trial, 93 patients with dysphagia and active esophageal eosinophilia aged between 11 and 40 years were randomized to receive either BOS 2 mg or placebo twice daily [18]. After 12 weeks, 39% of patients allocated to BOS, but only 3% of those who received placebo, achieved histological disease remission, defined as having ≤6 eosinophils per high-power field at all esophageal thirds. As for symptoms, the change in the validated Dysphagia Symptom Questionnaire (DSQ) score was significantly greater among patients treated with the active drug. There was one case each of esophageal and oral candidiasis in the BOS group; no differences between groups in cortisol levels or growth characteristics (for those aged younger than 18 years) were noted among study groups.

Results of a subsequent phase 3 trial with BOS have been made available very recently [103]: Overall 318 patients aged 11–55 years-old with active EoE were randomized 2:1 to receive BOS, 2 mg twice daily, or placebo for 12 weeks at academic or community care practices throughout the USA. BOS therapy was significantly superior to placebo in achieving histological remission (≤6 eosinophils per high-power field) (53.1% vs. 1.0%, respectively) and symptomatic improvement (≥30% reduction in the DSQ score) (52.6% vs. 39.1%; respectively). Significant improvements were also demonstrated in endoscopic and histopathological scores among patients allocated to the active drug compared to placebo. As for safety matters, esophageal candidiasis (3.8% vs. 1.9%) and oral candidiasis (3.8% vs. 0.0%) were more common with BOS, with no differences in abnormal ACTH stimulation test results (2.8% vs 2.9%, for patients under BOS and placebo, respectively).

Full responder patients enrolled in this phase 3 trial (those exhibiting ≤6 eosinophils per high-power field and ≥30% reduction in the DSQ score) to BOS 2 mg twice daily were, later on, randomized to blindly continue BOS or withdraw to placebo for 36 weeks [104]: EoE relapse was higher among patients who continued to placebo (43.5% vs. 24%), thus demonstrating some benefit for this compound in maintaining disease remission. In case of getting FDA approval, this budesonide compound could represent the first U.S. pharmacological therapy for EoE and the first drug to arrive on the U.S. market for adolescent and adult EoE patients.

As for Europe, an ongoing phase 2/3 trial is assessing the effectiveness and safety of different doses of a muco-adherent oral suspension of budesonide, specifically designed for EoE to induce clinical and histological remission of this disease in patients aged 2 to 17 year-old (EudraCT No. 2017–003737-29).

In order to make STC therapy more convenient for patients, an interest in simplifying the dosage of STC to single daily intakes has also arisen, with three different formulations currently being assessed:

APT-1011 is an orodispersible fluticasone tablet, which is being developed to treat EoE. After demonstrating safety, tolerability, and preliminary proof of effectiveness [105], the FLUTicasone in EoE (FLUTE) phase 2b trial (EudraCT No. 2016–004749-10) randomly allocated 103 patients to 4 fluticasone dosages ranging from 1.5 to 6 mg daily, the total daily dose taken either twice or once daily [106]. After demonstrating the 3 mg once daily dose as that which maximized the benefit/risk ratio (with 80% of patients having ≤6 eosinophils per high-power field after 12 weeks of therapy), an ongoing two-part, phase 3 trial (FLUTE-2) is currently evaluating the effectiveness of this medication in inducing and maintaining EoE remission in adult patients (ClinicalTrials.gov Identifier NCT04281108), with a sub-study also being carried out in adolescents (the FLUTEEN trial; NCT05083312), at several U.S. and European sites.

The second development involves the intake of 2 mg BOT once daily, instead of 1 mg twice daily, to induce remission of active EoE in adult patients: A phase-III non-inferiority trial is currently assessing the ability of both schemes to induce histological remission in adults with EoE (EudraCT No. 2020-001314-37).

The EsoCap system is a novel, smart drug delivery technology that potentially enables targeted and long-lasting local therapy of the esophagus [107]. The system consists of a hard gelatin capsule that contains a rolled mucoadhesive polymer film, which unfolds after been swallowed, thus enabling targeted placement of medication on the esophageal mucosa. Although EsoCap potentially treats different esophageal diseases, EoE has been selected for the first clinical application of the device through the ACESO trial – a phase 2 RCT to investigate the efficacy, tolerability, and safety of EsoCap containing mometasone 800 µg, applied once daily, compared to placebo, to induce remission in adult patients with active EoE (NCT04849390).

The possibility of maintaining prolonged remission of EoE through intermittent versus continuous treatment is an aspect that is currently being investigated: a phase 3 RCT is assessing the superiority of an intermittent and/or a continuous 48-week treatment with BOT, compared to placebo, for maintaining clinico-histological remission in adult and adolescent patients with EoE (EudraCT No. 2017–003516-39). Its results will be critical in informing the best strategies to maintain EoE remission in the future. Table 2 summarizes novel STC for EoE currently being developed through randomized clinical trials.

Even though most of the aforementioned studies are still being conducted and definitive data is not yet available, ongoing research on new drug development and dose optimization will consolidate STC therapy as the best studied therapy for EoE and the standard reference for alternative treatment options in EoE.

## 6. Targeted therapies and their potential role in improving EoE outcomes

Current therapeutic approaches are able to provide many patients with EoE histological and symptomatic remission. However, none of the current therapies have demonstrated the ability to modify the natural history of EoE, and the disease generally recurs after treatment cessation. In addition, the proportion of patients who still remain without an adequate treatment option and the growing epidemiology of EoE have generated a great interest in researching new therapeutic targets and developing new drugs.

The pathogenic mechanism in EoE is sustained by an inflammatory process driven by Th2 cells [108], type 2 innate lymphoid cells and type 2 cytokines, which include IL-4, IL-5,

Table 2. Novel swallowed topical steroids for eosinophilic esophagitis 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 |
| BOS (EudraCT 2017–003737-29) | Children and Adolescents | BOS dose adjusted to age vs. placebo | 2/3 | DB + OLE 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.

IL-9 and IL-13109. The interaction of a single cytokine with its specific receptor generates intracellular signals that are transduced through the Janus kinase (JAK), which phosphorylates signal transducer and activator of transcription (STAT) factors. After phosphorylation, STAT can form dimers that are transferred to the nucleus where they regulate the expression of cytokine-responsive genes by combining with specific DNA elements [110], thus regulating multiple biological processes.

Eosinophilic infiltration characterizing EoE is also common to other atopic conditions [108,109] in which a dysfunction of the epithelial barrier allows the interaction between allergens and inflammatory cells within the esophageal mucosa [111]. The esophageal epithelium is also the main source for thymic stromal lymphopoietin (TSLP), another JAK-dependent cytokine that plays an important role in type 2 diseases, serving as an alarmin upstream of Th2 cytokine production [112]. A central role has also been recognized for TSLP in EoE, which shows an increased expression in the esophageal tissues of patients, while TSLP receptor-deficient mice are protected from experimentally derived EoE [113]. Table 3 summarizes novel advanced therapies currently being investigated for EoE.

## 7. Targeting Th2 type inflammation in EoE with monoclonal antibodies

Together with eosinophils, the inflammatory infiltration in EoE includes dendritic cells, mast cells, and T cells, and its role is regulated by Th2 cytokines and eotaxins. Several biological agents based on monoclonal antibodies (mAbs), mostly imported from other Th2-mediated allergic diseases, are being investigated as being potentially effective in EoE, with a possible disease modifying effect, making them very attractive for a chronic disease. In eosinophilic asthma, eosinophils increase in the peripheral circulation and accumulate in the airway wall and lumen, causing mucus hypersecretion, bronchoconstriction and airway remodeling [114]. Asthma biological modifiers are therefore suggested as effective therapies for EoE and several mAbs targeting Th-2 cytokines are being investigated.

### *7.1. Blocking the IL-5 pathway to deplete eosinophilic infiltration*

IL-5 was one of the first therapeutic targets to be tested in EoE, due to its central role as a selective mediator in eosinophil proliferation, maturation, and activation [109]. Mepolizumab, reslizumab, and benralizumab are three mAbs that reduce eosinophilic inflammation and are recommended as add-on therapies for the treatment of patients with severe, uncontrolled eosinophilic asthma [115,116] and nasal polyposis [117]. Patients with active EoE also show upregulated levels of IL-5 gene and its protein in esophageal biopsies [77,108], and their blood-circulating lymphocytes produce significantly higher amounts of IL-5 following *in vitro* stimulation [118]. Therefore, investigation of this molecular target in EoE was granted.

Three RCTs evaluated the IL-5 blockers mepolizumab and reslizumab in EoE patients one decade ago [119–121]. The first drug was assessed in children and adults, and the second exclusively in children. Despite both drugs being effective in reducing blood and esophageal eosinophilia, peak eosinophil counts remained over 20 eos/hpf in all patients, and no histological remission was observed. A dose–response relationship could not be demonstrated for reslizumab [121]. As per symptom relief, none was superior to placebo. More recently, the open-label extension of the pediatric trial with reslizumab showed that the eosinophil count trended to improve over time, despite patients following a relatively unrestricted diet [122], thus suggesting certain biological effects in the long term. However, symptoms did not reduce compared to placebo.

Benralizumab is a more promising antibody which, instead of blocking soluble IL-5, is directed against the α chain of the IL-5 receptor (IL5RA), which enhances antibody-dependent cellular cytotoxicity and reduces eosinophils [123]. It has been approved to treat eosinophilic asthma in adolescents and adults, after demonstrating a superior effectiveness when compared to IL-5 blockers [124], and also providing benefit to patients with, among other conditions, hypereosinophilic syndrome [125] and EoE [126]. It is suggested that benralizumab normalizes the function of gastrointestinal eosinophils and improves digestive symptoms, and endoscopic features, as well as additional markers of disease activity. The effects of beralizumab are being investigated in eosinophilic gastritis in an on-going placebo-controlled RCT (NCT03473977) began in 2018. Recently, a phase 3 RCT was started in adolescent and adult patients with active EoE to compare the effectiveness of this drug, over placebo, on EoE histopathology and symptoms along a 24-week course of treatment, followed by a 28-week open-label period (NCT04543409).

### *7.2. Understanding the role of the IL-13 pathway in EoE*

IL-13 represents another attractive target for EoE, as this Th2 cytokine plays a key part in several eosinophilic inflammatory

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-controlledRCT | 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 |
| Dupilumab (NCT04394351) | Children | 3 | DB+OLE Placebo-controlled RCT | IL-4 receptor α monoclonal antibody (anti IL-4/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.

disorders. It has an important role in goblet cells hyperplasia and airway remodeling [127], including asthma and EoE. Unfortunately, several monoclonal antibodies targeting IL-13 (lebrikizumab, tralokinumab) were not able to reduce asthma exacerbations in phase-2 and phase-3 trials [128–130]. Despite this, there is still a place for anti-IL-3 mAbs in EoE: The expression of the IL-13 gene is up-regulated in blood eosinophils and in the esophageal mucosa of EoE patients, and is involved in eosinophil recruitment, subepithelial remodeling, and fibrosis [131]. IL-13 promotes epithelial dysfunction by decreasing gene expression of desmosome proteins, basement membrane components and adhesion molecules, and stimulates the expression and secretion by esophageal cells of eosinophil-activating chemo-attractants eotaxin-1/CCL11 and eotaxin-3/CCL26, which are responsible for eosinophil recruitment and accumulation in the esophageal epitelium [109].

Dectrekumab (QZX576) was the first mAb targeting IL-13 to be investigated as a potential treatment of adult EoE through a placebo-controlled phase 2 RCT [132]: Despite an intravenous (IV) infusion of QAX576 decreasing esophageal eosinophil counts, no patient achieved histological remission of the disease. In addition, no significant improvement in symptoms was documented, despite the therapy normalizing the expression levels of some EoE-related genes. After these limited results, the development of QAX576 in EoE was discontinued.

Cendakimab (also referred to as RPC4046 or CC-93538) was the second mAb blocking IL-13 to be assessed in EoE: A placebo controlled phase 2 RCT [61] compared two weekly subcutaneous (SC) injectable doses of cendakimab with placebo in treating active EoE. Overall, 99 adult patients were randomized to receive either cendakimab at high doses (360 mg), cendakimab at low doses (180 mg), or placebo in a 1:1:1 ratio for 16 weeks of therapy, followed by an optional open-label extension with the higher dose. After the 16-week double-blind period, reductions in mean eosinophil counts were statistically significant in both cendakimab groups compared to placebo, with 50% of patients treated with either active drug dose having less than 15 peak eos/hpf, while no patient under placebo achieved this goal ($p < 0.0001$ for both comparisons). In addition, 25% of patients in the cendakimab low-dose group and 20% in the high-dose group reduced peak cell counts to <6 eos/hpf after treatment. A non-significant trend toward symptoms improvement was noted in favor of RPC4046, particularly in dysphagia. Cendakimab was effective even in patients who had previously failed STC therapy. The open-label extension study showed a sustained symptomatic and histological improvement at week 52, following successful induction therapy among patients treated with the 360 mg dose [133]. As per safety concerns, mild adverse effects were observed with similar frequency in patients receiving treatment and placebo, with the most common adverse events being headache and upper respiratory tract infection. Further investigations on RPC4046 are currently being conducted through two different studies in adult and adolescent patients with active EoE: A phase 3 RCT is evaluating the efficacy and safety of cendakimab administered during a 24-week induction followed by a 24-week maintenance phase; with patients being assigned to either 360 mg of active drug SC weekly for induction, followed by 360 mg SC once every other week for maintenance, 360 mg SC weekly for induction and maintenance, or placebo (NCT04753697). Lastly, an open-label phase 3 trial is evaluating the longer-term safety profile and durability of response to the administration of a once weekly dose of CC-93538 (NCT04991935). No results from these trials are available to date.

### 7.3. Targeting the IL-4/IL-13 pathways: a promising approach

In-depth attention has been dedicated to IL-4 and IL-13. They have been clearly identified as preferential therapeutic targets since they play a central role in the pathogenesis of several type 2 inflammation disorders, including bronchial asthma, atopic dermatitis, and chronic rhinosinusitis with or without nasal polyposis. Both cytokines and their regulatory pathways also represent ideal therapeutic targets for treating EoE. Different to IL-13, IL-4 is not over-expressed in the esophageal mucosa of patients with EoE [134], but both cytokines are closely related, as they share one third of their gene sequences, bind to a common heterodimer receptor complex (IL-4Rα and IL-13Rα1) and exert overlapping biological effects [135]. Therefore, therapies targeting IL-4 and IL-13 separately

could be ineffective, and mAbs directed at blocking the effect of both cytokines have been clearly identified as preferential therapeutic targets toward improving results.

Dupilumab is a fully human mAb directed toward the α chain of the IL-4 receptor used by both cytokines, and has proved effective in treating all type 2 related diseases. After being demonstrated to: significantly reduce severe asthma exacerbations and improve lung function [136]; improve severe atopic dermatitis [137]; and rapidly decrease polyp size, radiological sinus opacification and symptom severity in chronic rhinosinusitis with nasal polyps [138], dupilumab is now being evaluated in EoE through on-going trials. The effectiveness of weekly SC doses of dupilumab to relieve dysphagia in adult patients with active, moderate-to-severe EoE was demonstrated in a phase-2 trial [139]: In this study, 47 adult participants were randomized to receive SC injections of either dupilumab at a 600 mg loading dose followed by 300 mg weekly, or placebo, during a 12-week double-blind phase. A significant improvement in the ability to swallow was reported by patients treated with dupilumab compared to placebo by week 10 (45% vs. 19% improvement from baseline in the Straumann's Dysphagia Symptoms Score [140]; $p < 0.05$). As per esophageal eosinophil counts, there was a significant decrease of 107% from baseline in patients who received dupilumab compared with an increase of 14% in those who received placebo. Overall, 82.6% of patients had their peak eosinophil counts reduced below 15 eos/hpf, and 65.2% had less than 6 eos/hpf. A significant improvement was observed in the endoscopic and histological activity scores of EoE in patients receiving dupilumab. Esophageal distensibility was also improved with dupilumab, compared with placebo, at week 12, measured by endoFLIP. Tolerability for dupilumab was good, with no serious adverse events; the most common event being injection site erythema and nasopharyngitis.

A large phase 3 RCT (NCT03633617) has recently been undertaken to determine long-term efficacy and safety of dupilumab. Adults and adolescent patients with active EoE were randomized to receive dupilumab 300 mg doses administered every week or every 2 weeks or placebo for a 24-week double-blind phase, after which histological and clinical measures were assessed. After that, all participants followed a 28-week extended phase with active treatment. Partial results of this trial have been reported to date: Significant improvements in symptoms (measured with the validated Dysphagia Symptoms Questionnaire [141]) were demonstrated from the second dose among patients allocated to dupilumab 300 mg weekly, compared to placebo; at week 24, 60% of patients achieved the histological endpoint of <6 eos/hpf; the beneficial effects of this dose were maintained up to week 52 [142]. A second phase 3 RCT (NCT04394351) is currently assessing the efficacy of dupilumab, compared with placebo, in pediatric patients with active EoE based on histological improvement. Here, patients are randomized to receive either placebo or a high or low dose of dupilumab SC injection, at tiered dosing regimens based on body weight, during a first 16-week double-blind phase, followed by a 36-week extended active treatment period, at which all patients will receive dupilumab SC injection at tiered dosing regimens based on body weight. Dupilumab is also being evaluated for the treatment of eosinophilic gastritis through a phase 2 RCT (NCT03678545).

### 7.4. Thymic stromal lymphopoietin and alarmins as possible therapeutic targets

The epithelial cytokines, including TSLP, IL-25, and IL-33, are early mediators at the top of the inflammatory cascade [143]. After being released from the airway or the esophageal epithelium in response to triggers, the broad inflammatory response involving IL-4, IL-5 and IL-13 that ultimately results in disease exacerbation (eosinophilic inflammation, smooth muscle contraction, and mucus production) is initiated [144]. Therefore, the central, upstream role of these epithelial cytokines has identified them as a strong potential therapeutic target in Th-2-mediated diseases and a second generation of biological agents has just started to be developed.

Tezepelumab is a fully human anti-TSLP antibody that has shown favorable effects in adult patients with severe uncontrolled asthma: Three different doses of tezepelumab or placebo were administered in a phase 2b RCT over 52 weeks. Tezepelumab was well tolerated and significantly reduced asthma exacerbation rates, blood eosinophil counts from baseline and pulmonary function [145]. Serum levels of Th2 cytokines were reduced as early as 4 weeks after treatment initiation and maintained throughout the 52-week treatment period. Ongoing trials are currently assessing the effectiveness of tezepelumab in severe chronic rhinosinusitis with nasal polyposis, atopic dermatitis, and chronic urticaria. Despite no trial on EoE yet investigating this drug, it has been shown that anti-TSLP antibodies or antibodies that inhibit its receptor (TSLPR) can block esophageal eosinophilia and food impactions in experimental EoE [113], and thus opens the door to new clinical investigations in patients with EoE.

## 8. The potential of inhibiting JAK-STAT signaling as a therapy for EoE

Janus kinase (JAK) inhibitor drugs block the tyrosine kinases involved in the signaling of T cell receptors and those of several cytokines that play a pivotal role in immune-mediated and allergic diseases. As JAKs regulate multiple biological processes, including many aspects of both innate and adaptive immunity, JAK inhibitors are now largely used for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases (IBD) [146,147]. Substantial preclinical data supports the potential benefit of inhibiting JAK to ameliorate airway inflammation and hyper-reactivity in asthma [148], where the inhaled route has been sufficiently demonstrated to inhibit airway inflammation in animal models of the disease [149], while avoiding the adverse effects associated with JAK inhibition by oral route. In the particular case of EoE, JAK-STAT6 pathway inhibitors have been demonstrated to block the secretion of eotaxin-3 (the major chemoattractant for eosinophils in this disease) by epithelial cells and lamina propria fibroblasts *in vitro* [150]. Although no study is yet formally planned in

EoE, the effectiveness of the JAK inhibitor tofacitinib to induce clinical and endoscopic remission and to significantly reduce esophageal eosinophilic infiltration in a patient with all treatment-resistant EoE has already been reported [151].

Studies in patients with IBD and rheumatic diseases have provided data on the safety profile of JAK inhibitors: In real-world patients with ulcerative colitis treated with standard doses of tofacitinib, mild infection (13%) was the most commonly adverse event found in a recent systematic review [152]. Upadacitinib also produced increased risks for herpes zoster and opportunistic infections compared to adalimumab among patients with psoriatic arthritis [153]. Concerns on an increased frequency of major adverse events when tofacitinib was used at higher doses have recently arisen, especially in patients with rheumatoid arthritis, cardiovascular events being of special significance [154]. In contrast, a subsequent meta-analysis summarizing 42 RCT carried out in patients with rheumatoid arthritis found that the risk of venous thromboembolism was reduced in patients treated with tofacitinib compared to placebo [155], thus highlighting the utmost importance of postmarketing pharmacovigilance in establishing the long-term safety of these drugs.

## 9. Targeting sphingosine-1-phosphate signaling: beyond immune-mediated diseases

Sphingosine-1-phosphate (S1P) is a signaling lipid that regulates T-cell trafficking as well as other cellular processes through S1P receptors (S1PR1-S1PR5). S1P receptors are involved in several cellular and physiological events, including lymphocyte/hematopoietic cell trafficking. Since lymphocytes live long and recirculate thousands of times, the S1P-S1PR pathway is involved in the pathogenesis of immune-mediated diseases [156]. Targeting S1PRs as a therapeutic strategy was first approved for multiple sclerosis, but new S1PR modulators are being evaluated to treat other immune-mediated diseases, including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis [157]. In EoE, naive T cells circulate through secondary lymphoid organs until they encounter their cognate antigen presented by dendritic cells in gut-associated lymphoid tissue. This interaction leads to the activation, proliferation, and imprinting of T cells with an esophageal localization phenotype through the up-regulation of specific adhesion molecules. Upon recirculation, these T cell subsets may subsequently migrate to the esophagus as its target tissue, where they initiate the process of homing. By blocking this lymphocyte recirculation, etrasimod can potentially exert a therapeutic effect in EoE. The safety and effectiveness of etrasimod (APD334), a selective ligand of S1P1R1, S1PR4, and S1PR5 is currently being studied in EoE in a phase 2 RCT (NCT04682639): Ninety-six adult patients will be randomly allocated to two dosages of etrasimod or placebo once for 24 weeks; followed by an additional 28-week extension treatment period. Results are expected to be available by February 2023. The advantages of oral administration of S1PR modulators and its potential effectiveness on different immunoallergic-based diseases, which frequently occur in the same patient, could displace mAbs in the treatment of EoE, if comparable effectiveness is confirmed.

## 10. Future potential therapeutic approaches for EoE

A better understanding of the pathogenesis of EoE is opening the way for new molecular therapeutic target research. New lines of investigation on novel treatment options are mainly aimed at decreasing tissue eosinophilia by inducing cell apoptosis, reducing the trafficking of eosinophils toward the esophageal mucosa, restoring epithelial barrier dysfunction and reversing fibrous remodeling.

### 10.1. 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. They are found primarily on the surface of immune cells, where they play a role in cell signaling and immune system regulation. Human eosinophils, mast cells, and, to a lesser extent, basophils preferentially express the inhibitory receptor Siglec-8 [158], which is involved in eosinophil apoptosis and clearance, inhibition of mast cell-released mediators, and reversal of tissue remodeling. Lirentelimab (AK002), an investigational mAb that targets Siglec-8, has been studied in a phase 2 RCT in patients with eosinophilic gastritis and duodenitis [159]: All lirentelimab dose arms in this trial showed statistical significance when compared to placebo in reducing gastrointestinal tissue eosinophil counts and patient-reported disease symptoms. Lirentelimab was generally well tolerated and the only treatment emergent adverse event occurring more frequently in lirentelimab than in placebo was mild-to-moderate infusion-related reactions. Although we have some results of phase-3 trials with AK002 in patients with eosinophilic gastritis or duodenitis (NCT04322604 and NCT0485689), an additional phase 2/3 study (KRYPTOS) is being carried out in patients with eosinophilic esophagitis (NCT04322708): 277 patients will be randomized to receive 6 monthly doses of either 1 mg/kg of lirentelimab, 3 mg/kg of lirentelimab, or placebo. Topline data from these studies were expected in the fourth quarter of 2021.

### 10.2. Blocking the action of eotaxins, the main eosinophil chemoattractants

Eotaxins are chemokines responsible for eosinophil recruitment via the CCR3 receptors. Apart from being the most well-known eosinophil-specific chemoattractants, eotaxin-3 secreted by epithelial cells was the most upregulated gene in the esophageal mucosa of patients with active EoE [160]. The administration of a CCR3 antibody to mouse models has been shown to inhibit eosinophil inflammation and mucosal injury in eosinophilic gastroenteritis [161], but showed no efficacy when studied in airway eosinophilia [162]. Studies with these drugs have not been proposed in EoE to date.

### 10.3. Calcium channels as regulators for esophageal eosinophilia

The ability of verapamil, a calcium-channel blocker, to reduce eotaxin-3 expression in esophageal cells *in vitro* has recently been demonstrated [163]. In addition, it has been recently

found that in EoE Th2 cytokines increase eotaxin-3 secretion in esophageal squamous cells through effects on intracellular calcium channels [164]. This finding places calcium channels and the regulation of eotaxin-mediated eosinophil recruitment as a promising target in the treatment of EoE, but there is no clinical data available yet and further research is needed.

### 10.4. Reversing and avoiding fibrous remodeling in EoE

Main long-term sequelae in EoE are caused by esophageal fibrous remodeling. Understanding mechanisms underlying collagen deposition in subepithelial tissue is a challenging goal, the prevention and treatment of it only having been addressed by a few studies [165]. An increased expression of transforming growth factor–beta (TGF-β) has been found in the esophageal mucosa of patients with EoE [119,166–168] which plays a central role to this cytokine in the formation of esophageal rings and narrow caliber esophagi. Reversal of fibrosis is currently recognized as a relevant therapeutic goal in EoE [41] and begins to be considered as a secondary end-point in the most recent RCT. Along with the available real-world observations showing that effective anti-inflammatory treatment with STC, diet [169], and PPIs [170] is capable of improving esophageal compliance, measured by using endoFLIP (a high-resolution impedance planimetry system), orodispersible tablets of budesonide [171] and dupilumab [139] have also shown the ability to reverse fibrous remodeling in EoE in the short term.

Losartan, an angiotensin II receptor blocker used to treat high blood pressure in children and adults, can reduce the signaling of TGF-β and, therefore, it appears to be a promising treatment for fibrosis in EoE [109]: Increasing doses of losartan have recently been tested in a phase 2 trial to evaluate endoscopic, histological, and symptomatic improvement in patients with EoE (NCT03029091).

## 11. Conclusion

Currently available treatment options for EoE are able to successfully control esophageal symptoms and inflammation in a proportion of patients, especially in the short term, but several limitations should be acknowledged. Intensive research is being developed for non-responder patients or for those with concomitant Th2-type conditions: new formulations of STC designed to optimally cover the esophageal mucosa; systemic biologics against various therapeutic targets; and small molecules that interfere in the signaling pathways of the inflammatory response in EoE; all aimed at reducing the impact of the disease on patients and their families.

## 12. Expert opinion

The therapy of EoE, more than any other aspect of the disease, has evolved significantly in recent years. The assessment of symptomatic and histological remission of EoE has presented a challenge because of the use of different criteria for effectiveness. In order to harmonize the reporting of treatment outcomes and allow comparisons among the different options, efforts are being made, encouraged by regulatory agencies [172], to reach an agreement on validated definitions for symptomatic, endoscopic, and histological remission, and to achieve homogeneity in the reporting of outcomes, with the use of validated instruments and guidelines [41].

Currently, first-line anti-inflammatory therapies for EoE includes diet, PPIs, and swallowed topical corticosteroids; in patients where these are effective, no one therapy offers a clear advantage over another in terms of histological and clinical remission in the short term. The choice of the initial and, especially the maintenance therapy, needs to be personalized according to the patients' needs and preferences, their personal and family life style, and the resources available to the provider. Long-term treatment strategy decisions should involve not only effectiveness, but also ensuring the maintenance of an adequate quality of life, avoidance of long-term fibrotic sequelae of EoE and adverse events derived from chronic use of medications or restrictive diets. Socioeconomic factors also need to be taken into consideration. Properly applied, the current available options allow successful management of a significant proportion of patients with EoE in terms of clinical, endoscopic and histological remission of the disease. The investigation and approval of novel esophageal-targeted formulas of topical corticosteroids will lead to refractoriness being limited to a minority of patients, especially when used to induce disease remission. Long-term benefit of the different therapies, including effects on maintaining high levels of health-related quality of life, however, are still unknown.

Despite current EoE treatment options having been shown to be effective in achieving disease control, they are not free of limitations. Dietary approaches, the only drug-free therapy that directly targets the primary cause of EoE, are controversial when it comes to long-term effectiveness. This is largely due to: lack of adherence; risk of developing IgE-type reactions after initial dietary elimination; economic costs and social burden; and their potential effect on quality of life [173]. Long-term viability of dietary restrictions will depend mostly on the number of foods eliminated and patient motivation. A pharmacological approach, however, could seem more appropriate for adolescents, due to their high level of non-adherence, and to avoid nutritional deficiencies in children as a result of extensive food elimination.

Despite not being specifically approved to treat EoE [174], PPIs represent an accessible and low-cost option, so they are widely used as a first-line treatment. However, PPIs are one of the least effective therapies, and not suitable for patients with stricturing EoE or with severe symptoms. Concerns over their long-term use have recently emerged, and they can interact with other medications. However, in real world, PPI has overwhelmingly been used as first-line therapy due to its convenience and safety, especially in young, otherwise healthy patients, such as those with EoE. The relative difficulties of dietary therapy management may obstruct its implementation as a first-line option in clinical practice.

Being equally effective as systemic steroids, STC have been shown to be safe for long-term use, even for children, with no significant risk of adrenal suppression or bone fracture – as shown in patients with asthma and ulcerative colitis [175–177]. New formulas of STC, designed to deliver the drug on the esophageal mucosa, may allow use of lower doses while still

maintaining EoE remission. Strategies to maintain remission with the lowest possible doses, or even with intermittent courses, should be investigated. Combining different treatments is not encouraged to date, as there is no evidence that it would enhance individual efficacy. Nevertheless, this approach needs to be explored further in patients partially responding to a single treatment.

Current options could be insufficient for some patients' groups, such as those refractory to STC administered in optimized formulas to target the esophageal mucosa, those who require high doses to maintain remission, or those who suffer from recurrent esophageal candidiasis. Patients with an extremely narrow-gauge esophagus present with a particularly severe form of EoE where it must be ensured that esophageal dilation is combined with highly effective anti-inflammatory therapies.

Novel biological agents and small immunomodulatory molecules effective in EoE have been proposed to overcome some of the limitations of current available therapies. They offer great therapeutic potential in relation to current pharmacological options, especially for refractory patients or those who require high doses. However, the risks of immune-mediated side effects derived from their mechanism of action are potentially significant, and they must be balanced against the benefits these drugs offer for EoE. Biological drugs targeting Th2-mediated inflammation have reported fewer side effects than 'classic' mAbs, but extended use and monitoring is required to evaluate long-term safety [178]. As EoE patients commonly have aeroallergen sensitization and concurrent Th2-mediated atopic diseases, including bronchial asthma, persistent allergic rhinitis, or difficult-to-control atopic dermatitis [179], novel biological therapies for EoE should be considered for those patients also suffering from other Th2-mediated diseases, as they could benefit from a single treatment simultaneously controlling several diseases. Undoubtedly, some of the different drugs that are currently being investigated to treat EoE and that are providing positive results, will be approved by the regulatory agencies in the near future. However, these products will significantly increase the cost of treating patients with EoE.

In the absence of pharmaco-economic and cost-utility studies, we must consider that EoE currently represents a significant burden on health care systems, in which a well-recognized diagnostic delay, the need for endoscopy with biopsies to diagnose the disease and monitor the response to treatments, and the costs of frequently ineffective therapies is estimated to be $ 2,300 per year in the U.S. [180]. This increases considerably, up to $ 4,001 per year, in pediatric patients, far exceeding the cost of care of Crohn's and celiac diseases [181]. Furthermore, admissions due to EoE or its complications are not infrequent, and their cost is high [182]. Therefore, it is possible that new drugs with proven efficacy are cost-effective [183], if they are able to simplify the management of EoE and avoid complications and the consumption of additional resources. The costs for healthcare systems and patient profiles will affect the possibility of incorporating these new drugs into real-world practice, as well as the potential of therapeutic schemes based on episodic versus maintenance therapy, or alternating treatment options at different stages of the disease.

To conclude, treatment strategies for EoE should be individually discussed and decided upon using a patient-centered approach, following a shared decision-making model, and ensuring appropriate long-term monitoring. New effective drugs to treat EoE will be incorporated into clinical practice in the near future, the use of which should be based on rational and realistic strategies that take into account cost-benefit from the widest possible view. The growing understanding of the patho-physiology and natural history of EoE will promote the research of further therapeutic approaches. In the meantime, new promising therapies are emerging.

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