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*Review*

# Exploring Treatment Options for Eosinophilic Esophagitis

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**Abstract:** Eosinophilic esophagitis (EoE), a chronic inflammatory disease of the esophagus, has been increasing in incidence over the past several years. Mainstays of treatment include dietary modifications, steroids, proton pump inhibitors (PPIs), and endoscopic dilation, with the goal being to control disease progression, promote remission, and alleviate symptoms, such as dysphagia and food impaction. In addition to these well-known treatment options, preliminary studies on new medications that target specific inflammatory mediators involved in the pathogenesis of EoE have shown promise in improving symptoms. This review article summarizes and discusses the application and efficacy of long-standing and promising new treatment options for EoE.

**Keywords:** eosinophilic esophagitis; EoE; elimination diet; corticosteroids; proton pump inhibitors; dilation



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## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory and immune-mediated disease of the esophagus characterized by eosinophilic infiltration of the esophageal epithelium. In 2018, this disease was found to affect 34.4/100,000 people with a steadily increasing incidence [1]. The current literature has recognized the highest prevalence of the condition in middle-aged Caucasian males; however, a diagnosis of EoE should be considered in any patient presenting with symptoms of dysphagia, regardless of age, race, or sex. In addition to dysphagia, patients with EoE also typically present with symptoms of food impaction, heart burn, regurgitation, vomiting, and chest pain [2,3]. Interestingly, adults and children may have different manifestations of the disease. Adults often present with symptoms of dysphagia and food impaction, while children are more likely to present with nonspecific symptoms, such as feeding disturbances and symptoms similar to those seen in gastroesophageal reflux disease (GERD) [1]. Although the dominant symptoms of adults and children are different, there are many similarities between the two groups, particularly in their associated comorbid conditions. For example, a history of atopic conditions, such as asthma, allergic rhinitis, atopic dermatitis, and environmental and food allergies, are commonly seen in both adults and children with EoE.

O'Shea et al. [4] suggested that disease development is multifactorial and stems from atopic, genetic, and environmental cues. Specifically, it is suspected that the esophageal inflammation resulting from exposure to certain allergens leads to the eosinophilic predominance found on biopsy in this condition. In particular, it has been hypothesized that these food allergens precipitate a T-helper type 2 (Th2) response in certain people, which leads to the production of many cytokines, such as Interleukin-5 (IL-5) and Interleukin-13 (IL-13), that then promote the creation of more downstream inflammatory mediators,

including periostin and eotaxin-3, that ultimately promote eosinophilic infiltration into the esophagus [5]. Due to this association with inflammatory mediators, monoclonal antibodies are currently under investigation as emerging treatment options for EoE. Similarly, several genes are currently being studied in association with EoE, such as Chemokine ligand 26 (CCL26), Calpain 14 (CAPN14), Thymic stromal lymphopoietin (TSLP), Signal Transducer and Activator of Transcription 6 (STAT6), and Leucine Rich Repeat Containing 32 (LRRC32), in hopes that this could further inform future treatment options. Additionally, recent research has shown the association of EoE with environmental risk factors, such as cesarean birth, formula feeding, certain antibiotic use, cold climates, and *Helicobacter pylori* colonization; the influence of the esophageal microbiota has also been researched, but its role remains unclear [2,4]. Importantly, EoE develops due to a combination of tissue remodeling, loss of barrier defenses, and eosinophilic inflammation. These processes are mediated by several cellular signaling molecules including Suppressor of Mothers against Decapentaplegic (SMAD), STAT6, and STAT5, each triggered independently by downstream activation of Th2 helper T cells and regulatory T cells by Interleukin-33 (IL-33) among others (Table 1) [4]. Nonetheless, much remains unknown, and further studies are being conducted to elucidate the exact mechanism by which EoE develops and progresses. Going forward, these studies are expected to inform further treatment that targets molecular pathways [4].

**Table 1.** Cellular signaling molecules and associated mechanisms with a role in the pathogenesis of EoE [4].

| Cellular Signaling Molecule | Induces | Mechanism |
|---|---|---|
| IL-4 | STAT6 | Important for inducing Th2 differentiation, which in turn plays a role in the secretion of TGF-beta, IL-4, IL-5, and IL-13 |
| IL-5 | | Promotes proliferation of eosinophils in the esophageal mucosa |
| IL-13 | Eotaxin-3 | Eosinophil chemotaxis via CCR3, a G-protein coupled receptor |
| | Periostin | Directly and indirectly stimulates adhesion and recruitment of eosinophils |
| IL-33 | | Promotes atopy |
| TGF-beta | pSMAD2pSMAD3 | Role in esophageal remodeling in the lamina propria, leading to esophageal fibrosis and strictures |

While the pathogenesis of EoE is complex, diagnosis is based on histological and clinical findings. In a patient presenting with dysphagia, food impaction, and other nonspecific upper GI complaints with a background of atopy or allergies, it is recommended to perform an esophagogastroduodenoscopy (EGD) for visualization and biopsy [3]. Evidence of disease is typically seen on endoscopy and varies based on age. In adults, EoE can appear as esophageal strictures and rings with associated narrowing of the esophagus [6]. In contrast, children more often exhibit linear furrowing with white exudates and edema, although these features may also be seen in adults [3]. Regardless of age, an edematous and inflammatory appearance of the esophagus can indicate underlying EoE. The pathologic criteria for the diagnosis of EoE is the presence of 15 or more eosinophils per high power field on histologic exam of biopsy specimens [2,6]. Of note, it is pertinent to perform a workup for other causes of dysphagia, such as GERD and achalasia, to rule out additional disease processes [2]. Once these differential diagnoses are excluded in a symptomatic patient with biopsy findings suggestive of eosinophilia, a diagnosis of EoE can be confirmed.

After the diagnosis is made, it is important to explore treatment options, which classically include diet therapy, proton pump inhibitors (PPIs), and corticosteroids as necessary [2].

## 2. Dietary Modifications

Since EoE disproportionately affects patients with atopic disease, management with allergen avoidance therapies in lieu of corticosteroid use has been tried as an initial option and has been successful in many cases. In patients with food allergies in particular, elimination diets have proven to effectively reduce both the severity and progression of EoE. Regarding specific allergens, the six foods found to be most associated with EoE include cow's milk, wheat, eggs, soy, nuts, and seafood/shellfish [7,8]. Thus, a six-food elimination diet has been attempted, and it was found that adult patients subsequently had a decrease in dysphagia symptoms and reduction in eosinophil count on repeat endoscopy [8]. Furthermore, the reintroduction of the implicated foods resulted in rebound dysphagia within five days with an increased eosinophil count [8,9]. This finding was especially profound for wheat and cow's milk reintroduction, further supporting previous studies identifying them as the most common food triggers of EoE [8].

Another method of dietary management is the two-food elimination diet, in which patients are recommended to remove wheat and cow's milk from their diet first, followed by the four other common food triggers for residual symptoms. Based on the strong association of EoE with wheat and cow's milk, there had been a question of whether a two-food elimination diet or a six-food elimination diet would be more effective at improving symptoms. The 2-4-6 study was a multicenter prospective study in which patients observed a two-food elimination diet (cow's milk, wheat) for 6 weeks (Figure 1). Patients without symptomatic improvement or decreased eosinophil counts after 6 weeks followed with a four-food elimination diet (cow's milk, wheat, egg, soy). If this was also unsuccessful in improving symptoms and reducing eosinophil counts, patients were then asked to follow the six-food elimination diet (cow's milk, wheat, egg, soy, nuts, fish/seafood). Of 105 adult and 25 pediatric patients, 43% of participants showed complete symptom alleviation with the two-food diet [9]. Upon the reintroduction of the foods, it was found that EoE symptoms and eosinophilia reappeared within days of adding the removed food stimuli. The slow reintroduction of foods one by one allowed the identification of the specific allergenic stimuli of interest for each patient, and this information was used to personalize treatment. This approach not only outlined a manageable and effective diet plan for EoE patients, but also was estimated to reduce procedure rates and diagnostic time by 20% [9].


**Figure 1.** Outline of the 2-4-6 study for stepwise food elimination and diet organization.

Since food allergy and EoE are increasingly recognized as related conditions, elimination diets provide an effective management option. Though several diet plans have been considered, the 2-4-6 study suggests an elimination diet that decreases the utilization of healthcare resources while also personalizing a diet plan to the food triggers of each patient [9]. This personalized diet may be easier to follow than the standard six-food elimination plan and may result in reduced disease remission due to increased pa-

tient adherence [9]. Thus, food allergen identification should be considered for patients with EoE.

### 3. Steroids and PPI Use

While dietary management may prove to be successful in some patients, medical management is often necessary, which is frequently done with corticosteroid therapy. According to the 2020 Clinical Practice Guidelines by the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters, topical glucocorticoids are strongly recommended with moderate quality evidence and are recommended over oral glucocorticoids due to decreased side effects [10]. Examples of topical corticosteroids include budesonide or fluticasone given in a viscous solution to be swallowed twice daily [11]. Side effects of swallowed topical corticosteroids include esophageal candidiasis as well as oral candidiasis [11]. Several studies have shown corticosteroid therapy to be efficacious in the treatment of EoE [12–15]. For instance, Dellon et al. [13] performed a double-blinded clinical trial assessing 111 adults with EoE who were randomized to receive either fluticasone 880 ug swallowed twice daily or oral viscous budesonide 1 mg twice daily for eight weeks. Peak eosinophil counts were found to decline in both groups (73 to 15 eos/hpf in budesonide group and 77 to 21 eos/hpf in the fluticasone group). Histologic remission was also found in the majority of both the budesonide group (71%) and the fluticasone group (64%) [13]. In another study of 229 patients with EoE (with a median follow-up time of 5 years), swallowed topical corticosteroid use resulted in a higher frequency of clinical remission (31% to 4.5%), endoscopic remission (48.8% to 17.8%), and histologic remission (44.8% vs. 10.1%) compared to patients who were not swallowing the topical corticosteroid [12]. Lucendo et al. [14] performed a double-blind, parallel study of 88 EoE adult patients to assess the effectiveness and tolerability of a budesonide orodispersible tablet (BOT). The primary endpoint of the study was complete remission based on both clinical and histological factors, and the secondary endpoint was histologic remission. It was found that at the end of the six-week period, 58% of patients given BOT were in complete remission compared to 0% of the patients in the placebo group ($p < 0.0001$) and that 93% of patients achieved histologic remission. Of their study cohort, only 5% of patients developed symptomatic, mild candida of the esophagus, which was easily treated with proper antifungal therapy [14]. Overall, there has been much evidence in the literature supporting the use of corticosteroid therapy in the management of EoE with minimal side effects (Table 2).

Historically, prior to initiating therapy with corticosteroids, an eight-week PPI trial has been used to rule out GERD and diagnose EoE in patients presenting with symptoms of esophageal dysfunction, as these two conditions were believed to be mutually exclusive. However, it has been found that a large proportion of patients with esophageal symptoms and biopsy findings of over 15 eos/hpf responded to treatment with high dose PPIs but did not have a clinical presentation consistent with GERD. These patients came to be known as having PPI-responsive esophageal eosinophilia (PPI-REE), although this term is no longer recognized, as these patients were later found to be clinically and histologically indistinguishable from other patients with EoE [16]. It is now known that EoE and GERD are not mutually exclusive—that is, they coexist: EoE can lead to secondary reflux due to esophageal dysmotility, and GERD can lead to decreased epithelial barrier integrity, resulting in increased antigen exposure and inflammation. PPIs were also found to have other beneficial mechanisms of action in addition to decreasing acid production in the stomach, such as anti-inflammatory responses specific to eosinophils and the reversal of epithelial permeability. As a result of all these new findings, the 2018 diagnostic guidelines for EoE proposed to discontinue the use of the eight-week high dose PPI trial and instead recommended that PPIs be used as a form of therapy for EoE [16].

**Table 2.** Summary of a few studies analyzing steroid management. These studies were cited in particular because of the variation in type of steroid medication, dosing, and outcome measures.

| First Author | Publication Year | Population Type | Cases of EoE | Study Design | Study Period | Medication, ROA | Duration | Results |
|---|---|---|---|---|---|---|---|---|
| **Greuter** | 2018 | adult (mean age 39 +/− 15 years) | 229 | retrospective, single center | 2000–2014 | swallowed topical corticosteroid | induction txt with 1.0 mg BID (2–4 weeks until clinical response) followed by maintenance txt of 0.25 BID | Longer duration of STCs were found to have . . .<br>- endoscopic remission: 48.8% vs. 17.8% control ($p < 0.001$)<br>- clinical remission: 31.0% vs. 4.5% control ($p < 0.001$)<br>- histologic remission: 44.8% vs. 10.1% control ($p < 0.001$)<br>- complete remission: 16.1% vs. 1.3% control ($p < 0.001$) |
| **Dellon** | 2019 | adult (39 +/− 14.5) | 129 | randomized, double blind | | fluticasone MDI | 880 ug BID for 8 weeks | - reduction in peak eosinophil counts (77 to 21 eos/hpf)<br>- 64% had histologic response ($p = 0.38$) |
| | | adult (36 +/− 19) | | | | oral viscous budesonide | 1 mg BID for 8 weeks | - reduction in peak eosinophil counts (73 to 15 eos/hpf)<br>- 71% had histologic response ($p = 0.38$) |
| **Lucendo** | 2019 | adult (18–75 years) | 88 | randomized, double blind | NA | budesonide orodispersible tablets | 1 mg BID for 6 weeks | BOT group was found to have . . .<br>- 58% in complete remission ($p < 0.001$)<br>- 93% in histologic remission ($p < 0.001$) |
| **Straumann** | 2011 | adult (mean age 38 +/− 12 years) | 28 | randomized, double blind | NA | swallowed budesonide | 0.25 mg BID for 50 weeks | Low dose budesonide group was found to have . . .<br>- complete histologic remission: 35.7% vs. 0% control<br>- partial remission: 14.3% vs. 28.6% control<br>- decrease in mucosal thickness (0.75–0.45 mm, $p = 0.025$), but stable epithelial thickness (261.22 vs. 277.23 um, $p = 0.576$) |

Thus, EoE is often managed medically with proton-pump inhibitor therapy (PPIs), such as omeprazole and pantoprazole. PPIs have a longstanding safety profile as well as ease of administration. They are typically dosed at 20–40 mg or 1 mg/kg per dose twice daily in adults and children, respectively [17]. According to the 2020 Clinical Practice Guidelines by the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters, PPIs are recommended over no treatment as a conditional recommendation with very low-quality evidence [10]. These guidelines report that 23 observational studies evaluating a histologic response to PPIs found an unweighted histologic response rate of 42%, and that PPIs failed to induce histologic remission in about two-thirds of patients with EoE compared to >85% of controls [10]. With that being said, it has been suggested that PPIs may benefit some patients with esophageal eosinophilia and are a reasonable place to begin treatment given their safety and limited adverse effects [11].

In addition to their use as a primary treatment option, PPIs can also be given as adjunct therapy in patients with EoE, as there is a high prevalence of GERD in this population and the reduction in acid production can decrease inflammation and symptoms [18]. A study in 2014 assessed gene expression of eotaxin-3, IL-13, and IL-5 in the distal and proximal esophagus of consecutive adult patients with an EoE phenotype (dysphagia/food impaction, typical endoscopic findings and >15 eos/HPF) at baseline and after treatment with omeprazole 40 mg twice daily for 8 weeks [19]. This study found IL-13 and eotaxin-3 to be significantly decreased in both esophageal sites after eight weeks of PPI therapy, suggesting that PPIs have anti-inflammatory mechanisms of action. There have been several other studies noting the efficacy of PPIs in the treatment of EoE. For instance, a meta-analysis that included 33 studies of 188 children and 431 adults found a reduction in clinical and histologic disease in both groups (60.8% and 50.5% of patients, respectively) [20]. Another study assessed 121 patients with EoE and found that 33% achieved complete remission after 40 mg omeprazole twice daily for eight weeks, and 81% remained in complete remission after reducing the dose to 40 mg once daily. Of these patients, 83% remained in remission with just 20 mg omeprazole per day [21]. Overall, PPIs are an efficacious form of therapy in the management of EoE and deciding whether to pursue PPI therapy or steroids should be decided on an individualized basis.

## 4. Dilation

While dietary and medical management may offer relief to some patients, many individuals with eosinophilic esophagitis experience symptoms secondary to chronic inflammation (Figure 2). This chronic inflammation can lead to structural changes in the esophagus, which can both worsen current symptoms and cause new ones. It has been found that food impaction typically occurs once the diameter of the esophagus is less than 17 mm and that dysphagia typically occurs at less than 13 mm [22]. Furthermore, eosinophils may mediate tissue remodeling and cause subepithelial fibrosis, which can lead to or worsen existing dysphagia, food impaction, and motility issues [23]. Additionally, inflammatory cells may release factors, such as Transforming Growth Factor beta (TGF-beta), that contribute to esophageal remodeling [23]. Regardless of the method of tissue remodeling, these chronic inflammatory changes can lead to stricture formation, a severe and fairly common complication associated with EoE [3,24]. In patients that develop esophageal strictures unresponsive to medical management, endoscopic dilation is a treatment option (Figure 3) [25].

Esophageal endoscopic dilation is a procedure that involves the use of inflatable balloon dilators passed through an endoscope or endoscopically placed wire guided bougienage techniques to mechanically expand strictured areas of the esophagus [25]. Although this manipulation provides symptomatic relief, the underlying inflammation and histology remain unchanged [6]. Due to the lack of disease-modifying effects, dilation is typically used when dietary or medical therapy has been ineffective, or when a patient develops a complication due to remodeling, such as short-segment esophageal narrowing, like strictures, and/or long-segment esophageal narrowing, which includes trachealization,

ring formation, and long-segment stenosis [24]. In other words, dilation therapy is used when chronic inflammation has progressed to fibrosis and scar tissue deposition, which unfortunately are irreversible sequelae of EoE.

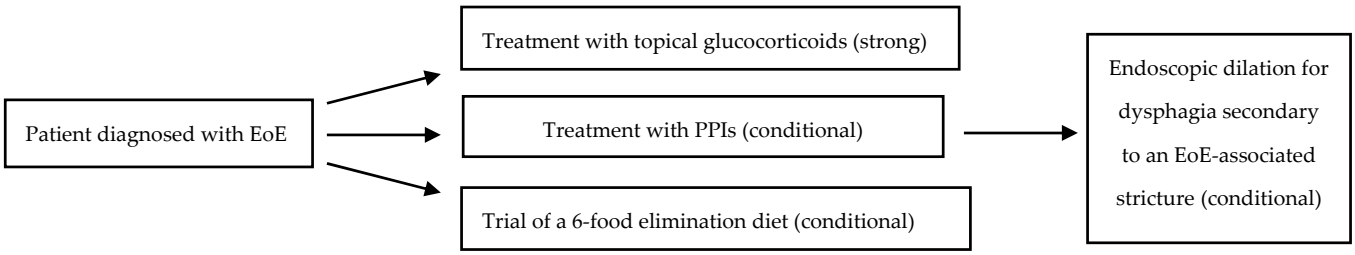


**Figure 2.** Flow chart of the clinical management of EoE, according to the AGA and JTF on Allergy–Immunology guidelines, including strength of recommendations [10].

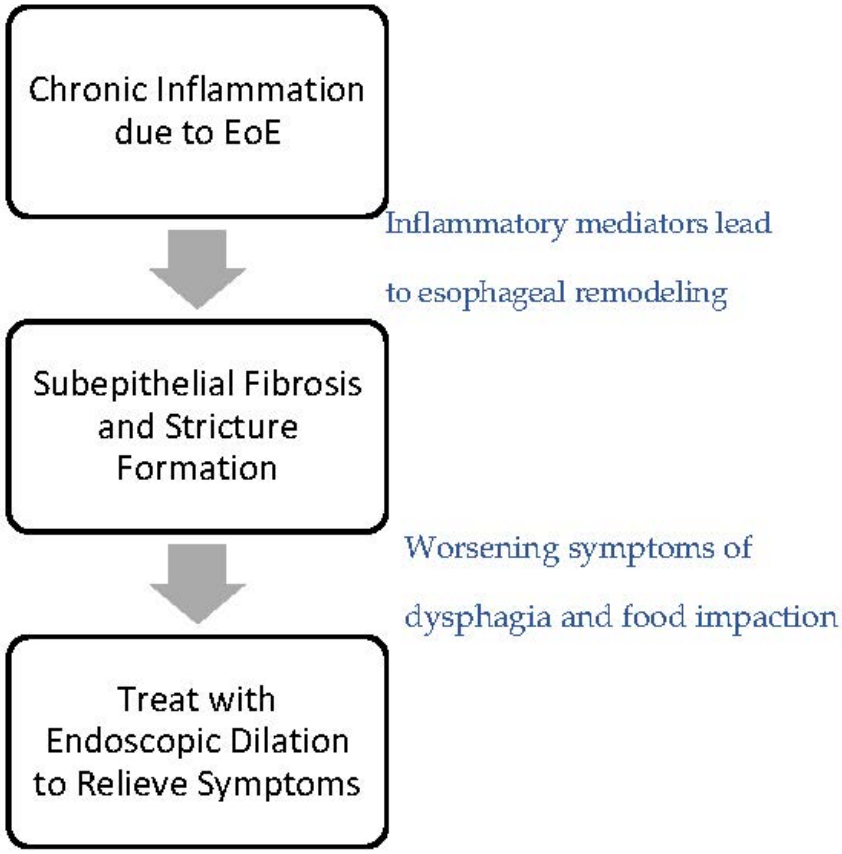


**Figure 3.** Schematic representation of the progression of EoE leading to the need for esophageal dilation.

Many studies have found esophageal dilation to be effective in relieving dysphagia, with beneficial effects persisting for over one year [26]. One study found that following esophageal dilations, 84.95% of people experienced improvement in their clinical symptoms, with a median follow-up of 12 months [27]. Surdea-Blaga et al. [22] found that 95% of patients with EoE experienced symptomatic improvement following endoscopic dilation. However, since this procedure does not affect the underlying cause of inflammation, many patients require multiple dilation procedures [6]. When this is the case, it is often recommended that patients undergo subsequent dilations 2–3 weeks apart, with the initial measurements of the esophageal diameter determining how many sessions will be necessary [11]. Furthermore, dilation appears to be well-tolerated by patients with many willing to pursue future dilations as needed [26].

Dilation has been found to be a relatively safe procedure [11,26–28]. Initially, prior studies indicated higher rates of endoscopic complications, such as tears or perforations, in patients with EoE than in patients undergoing dilation due to other underlying conditions [11]. However, recent research has found this not to be the case and has indicated that the most common side effect experienced is post-procedure chest pain that resolves without intervention [27]. Dellon et al. [26] reported that two meta-analyses found the rate of perforation after dilation for patients with EoE to be 0.3%, which is similar to rates seen with endoscopic dilation overall. Additionally, Moole et al. [27] found low rates of perforations (0.81%), deep mucosal tears (4.04%), hemorrhage (0.38%), and hospitalization (0.74%) [27].

## 5. Newer Treatment Options

While dietary, medical, and procedural management (steroids, PPIs, and dilation) result in symptomatic alleviation for many, newer treatment options continue to be investigated. Considering the similarity in pathophysiology of EoE and various atopic conditions (asthma, dermatitis, food allergies), monoclonal antibodies have shown some effectiveness in the management and prevention of EoE. These treatments bind inflammatory mediators, such as IL-3, IL-5, IL-13, Tumor Necrosis Factor alpha (TNF-α), and Immunoglobulin (Ig) E, to prevent activation of downstream inflammatory pathways [5].

A number of clinical trials have provided valuable information on the efficacy of these treatment alternatives. To start, RPC4046, a monoclonal antibody targeting IL-13, is a weekly subcutaneous injectable that showed initial clinical and histologic improvement in a pilot study [29]. A phase two trial found that both low-dose and high-dose RPC4046 decreased eosinophil count in the esophagus after 16 weeks. Additionally, patients reported improvement in disease severity, promising support of further trials of this treatment [30].

In addition to targeting IL-13, multiple treatments aimed at IL-5 have also found encouraging results. Reslizumab, a humanized monoclonal antibody that targets IL-5, has shown promise in reducing esophageal eosinophil counts [31]. Spergel et al. [31] performed a randomized, controlled clinical trial investigating reslizumab as a treatment option in 226 children and adults with EoE and found that the treatment groups had a statistically significant reduction in esophageal eosinophil count compared to the placebo group. However, this reduction in eosinophil count did not result in a statistically significant clinical difference, as both groups reported an improvement in symptoms and quality of life, so further research into this specific option is indicated to fully elucidate the effects. In addition to reslizumab, mepolizumab is another monoclonal antibody targeting IL-5 that has shown promise in early studies in patients with EoE [32]. In an open label phase one/two study of four patients, mepolizumab was found to improve clinical symptoms in all patients and result in endoscopic improvement in three of the four patients [32]. Another study of mepolizumab that included 11 adults, with 5 receiving mepolizumab and 6 receiving the placebo, found there to be a significant reduction in esophageal eosinophil count, but did not show considerable symptomatic improvement. Although both of these studies involved a small number of patients, they provide evidence of the potential therapeutic efficacy of these targeted treatment options [33]. Benralizumab is another antibody targeting IL-5 that is currently in a phase three trial investigating its effects in EoE, and it has previously been found to be effective in treating other eosinophilic conditions [34].

Lastly, dupilumab is an IL-4 and IL-13 inhibitor that has previously demonstrated efficacy in other atopic conditions [29]. A phase two study examining weekly subcutaneous injections of dupilumab found symptomatic improvement of dysphagia through increased distensibility of the esophagus with a resulting decrease in esophageal eosinophil counts [35]. Dupilumab continued to demonstrate efficacy and was approved by the FDA as a treatment for EoE in May of 2022, making it the first ever FDA-approved treatment for EoE. While most of this novel research is still in early stages, the expansion of treatment alternatives provides hope for improvement in patient outcomes.

## 6. Conclusions

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease that commonly presents with dysphagia, food impaction, heart burn, regurgitation, vomiting, and chest pain [2,3]. Due to the strong association between EoE and atopy, dietary management with food allergen avoidance is commonly utilized as an initial approach to prevent medication use. A six-food elimination diet has been found to decrease both the dysphagia symptoms and the eosinophil count on repeat endoscopy [7,8]. Thus, these diet plans tailored to individual patients may be a way to provide symptomatic relief and improved histologic findings in many patients [9]. When medical management is necessary, topical corticosteroids, such as budesonide or fluticasone, have been efficacious in providing both clinical and histologic remission in many patients [12–15]. PPIs, such as omeprazole or pantoprazole, are effective in the management of EoE especially for patients with concurrent GERD [18,20]. Once patients have developed the long-term sequelae of EoE, such as strictures, endoscopic dilation is the preferred method for symptomatic relief [11,23,27,28]. While the previously mentioned methods have typically been used to treat EoE, there are currently new treatment options being explored. Targeted therapy with monoclonal antibodies focuses on inflammatory mediators implicated in the disease process, such as IL-13 and IL-4 receptor alpha, and have shown promise in phase 2 clinical trials. While these developing therapies are promising, dietary modification, corticosteroids, and PPIs remain mainstays of current therapy. All are efficacious in reducing both clinical symptoms and histologic findings in patients with EoE. Treatment plans for patients with EoE should be individualized since the most beneficial approach will vary between patients.

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