



Biological Therapies for Eosinophilic Esophagitis: Where Do We Stand?

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Abstract

Eosinophilic esophagitis (EoE) is an immune-mediated, chronic esophageal disease characterized by esophageal symptoms and esophageal eosinophilia. It is triggered by foods and possibly by environmental allergens. Currently, there are no FDA-approved therapies for EoE. Commonly used treatments include dietary restrictions and topical corticosteroids. Many of these therapies are suboptimal in their efficacy, have side effects, or diminish patients' quality of life. Biologic therapies for EoE have therefore been sought as an alternative. The mechanism by which food allergens trigger EoE is thought to be a T helper type 2 (Th2) reaction, resulting in secretion of the cytokines IL-4, IL-5, and IL-13. IL-5 induces eosinophil production and trafficking to the esophagus, and IL-13 induces esophageal epithelial cells to secrete eotaxin-3, which drives eosinophil chemotaxis and activation. Mepolizumab and reslizumab, two anti-IL-5 antibodies, were studied in children and adults with EoE and resulted in reduction of esophageal tissue and blood eosinophils, but no significant reduction in symptoms. QAX576, an anti-IL-13 antibody, was studied in adults with EoE and showed a decrease in the esophageal eosinophil load and a trend towards clinical improvement. Since *in situ* IgE production was demonstrated in the EoE esophagus, omalizumab, an anti-IgE antibody, was studied in patients with EoE and not found to be overall beneficial. Furthermore, given the increased esophageal epithelial cell TNF- α expression in EoE, infliximab, an anti-TNF- α antibody, was studied in patients with EoE, with lack of success both clinically and histologically. In summary, although none of the biologicals studied so far in EoE have been highly effective, many demonstrated some histological benefit, especially those that targeted the Th2 axis. Therefore, the future for biologicals is promising as the pathophysiology of EoE is better understood, clinical assessment tools are validated, identification of patient subsets that respond best to biologicals is made, and dosages of biologicals are optimized.

Keywords Eosinophilic esophagitis · Biologic · Mepolizumab · Reslizumab · Omalizumab · Infliximab · QAX576 · T helper type 2 immunity · IL-13 · IL-15 · IgE · TNF- α

Abbreviations

CCR3	Chemokine receptor type 3
EoE	Eosinophilic esophagitis
HPF	High power field
IgE	Immunoglobulin E
IL	Interleukin
MDQ	Mayo dysphagia questionnaire
PPI	Proton pump inhibitor
Th2	T helper type 2
TNF- α	tumor necrosis factor- α

Introduction

Current Therapies Commonly Used in Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, T helper type 2 (Th2) immune-mediated esophageal disease that is receiving increasing recognition. This disease is diagnosed by clinical symptoms of esophageal dysfunction, histological evidence of eosinophilia that is limited to the esophagus with a minimum threshold of 15 eosinophils/high power field (HPF), and unresponsiveness to a high dose proton pump inhibitor (PPI) therapy trial for at least 8 weeks [1]. Clinical symptoms vary based on the age of the patient [2, 3]. In adults, symptoms include dysphagia, heartburn, chest pain, and food impactions. In pediatric patients, symptoms tend to be non-specific and include abdominal pain, nausea, vomiting, feeding refusal, and failure to thrive [4]. The inflammation in EoE is triggered by various foods and possibly by environmental

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allergens. Evidence for food triggers is repeatedly shown by inducing disease remission with food eliminations, followed by disease relapse with certain food re-introductions [5]. However, the nature of this immunological reaction is not that clear. It is believed to be a mix of immunoglobulin E (IgE)-mediated and non-IgE (Th2)-mediated hypersensitivity responses [1], although the evidence for an IgE-mediated mechanism is becoming less evident [6]. Currently, there are no FDA-approved therapies for EoE. Treatments commonly accepted and currently used consist of dietary restriction therapies and corticosteroids.

Dietary therapies currently used to treat EoE include the elemental diet, the test-directed elimination diet, and the empiric elimination diet. The elemental diet is a strict dietary treatment that consists of exclusively feeding the patient an amino acid-based formula in order to completely eliminate dietary antigens. It has been shown to be very effective in improving clinical symptoms and decreasing esophageal eosinophilia [7]. After reaching remission, foods are reintroduced into patients' diets. Although this dietary treatment has shown positive results, it is limiting on quality of life because of its restrictive nature, and the need for several repeat endoscopies when attempting to introduce foods back to the diet in the attempt of identifying triggers. Consumption of large volumes of amino acid-based formula is often needed to meet caloric requirement, which necessitates tube feeding in some patients [8]. The test-directed elimination diet utilizes skin prick and atopy patch testing in order to identify specific EoE food triggers, which are then removed from the patient's diet [9]. Skin prick tests are typically used to detect an immunoglobulin E (IgE)-mediated allergic reaction, and patch tests are typically reflective of a T cell delayed immunological reaction. This diet allows for more flexibility because only the specific foods that test positive are removed from the patient's diet and others can remain in the diet [8]. However, the efficacy of this diet has been very modest, as it resulted in a histological remission rate of < 50% in a recent meta-analysis [10]. The empiric elimination diet eliminates foods known to be common allergens from the patient's diet without any testing. If remission is achieved, foods are then reintroduced into the patient's diet one at a time with assessment of clinical symptoms and esophageal histology by endoscopy with esophageal biopsies. Historically, this diet started by eliminating six food groups from the patient's diet (milk, wheat, egg, soy, peanut/tree nuts, and fish/shellfish) [11, 12] and was then reduced to elimination of the four most common among these (milk, wheat, egg, and soy) [5, 13] and then more recently even the two most common (milk and wheat) [14]. Histological remission rates for the 6-food and 4-food elimination diets were reported at 74 and 64%, respectively, for children and 73 and 54%, respectively, for adults [5, 11–13]. Histological remission rates for the 2-food elimination diet were reported at 43% for children and adults [14].

However, these diets, even though less limiting than an elemental diet [8], are still very disruptive to some patients and require multiple endoscopies following remission to identify the food triggers.

Pharmacological therapies that are most commonly offered to patients suffering from EoE include systemic corticosteroids and topical corticosteroids. Systemic corticosteroids, specifically oral corticosteroids such as methylprednisolone or prednisone, have been shown to reduce esophageal eosinophilia and symptom severity and are often used for immediate relief of EoE symptoms [15]. There are many concerns about the use of oral corticosteroids. EoE is a chronic disease, and therefore, the use of oral corticosteroids would have to be long-term, which can lead to significant side effects such as osteoporosis [16]. Topical corticosteroids such as swallowed fluticasone and oral viscous budesonide are considered a safer alternative when treating EoE, though none are FDA-approved for EoE. Topical corticosteroids have been effective in inducing histological disease remission [17]. However, they are not without potential side effects, one of which is local in the form of oropharyngeal and/or esophageal candidiasis, and the other systemic, with concerns about possible adrenal suppression with higher doses are used, or when concurrent topical corticosteroids are used nasally or to inhale to treat allergic rhinitis or asthma. Furthermore, similar to the case with systemic corticosteroids, topical corticosteroids have to be administered for a prolonged period of time given the chronic nature of EoE, to prevent disease relapse [18], as discontinuation of the medication may later result in symptom relapse.

Given that EoE is a chronic disease with significant morbidity and a markedly diminished quality of life [19], and given the fact that current therapies are suboptimal either in their efficacy or their associated side effects, the need for alternative treatments is growing. Biologic therapies are potential alternative treatments for EoE patients, which may have a smaller impact on patients' lifestyles. These biological treatments are aimed at specifically targeting various parts of the inflammatory cascade in the esophagus of EoE patients.

Pathophysiology of Eosinophilic Esophagitis

The presence of eosinophilia in the esophagus is a defining feature of EoE because normally the esophagus is devoid of eosinophils. Multiple immune cells also infiltrate the esophagus of EoE patients, including lymphocytes, mast cells, and basophils, some of which have been shown to be activated [20]. A cytokine profile consistent with a Th2 phenotype suggests the allergic etiology of EoE [21, 22], including interleukin (IL)-4, IL-5, and IL-13. IL-4 is known to induce naïve T cells into Th2 cells and to activate B cell class switching to produce IgE, thus initiating a Th2-mediated immune response. IL-5 is produced by Th2 cells, mast cells, and eosinophils. While IL-5 is a cytokine that induces eosinophil production

and eosinophil trafficking to the esophagus in EoE [23], IL-13, produced by Th2 cells and activated eosinophils in EoE [21], was shown to induce esophageal epithelial cells to secrete eotaxin-3, which drives eosinophil chemotaxis and activation [22, 24]. Figure 1 illustrates what we understand regarding the pathophysiology of EoE, and how the various biologicals attempted so far can potentially disrupt the immunological reactions of EoE, hence potentially inducing disease remission. Below is a discussion of the various biologicals tested, guided by each potential target molecule implicated in EoE, which are also summarized in Table 1.

Molecules Implicated in EoE with Corresponding Biological Therapies

IL-5

IL-5 is a pro-inflammatory cytokine secreted by T lymphocytes, mast cells, and eosinophils. It is important in the development and differentiation of eosinophils, as well as their release from the bone marrow to the peripheral circulation

[32]. IL-5 also primes eosinophils to respond to chemoattractants such as eotaxin [33]. IL-5 plays a role in eosinophil trafficking to the esophagus. In studies conducted with mice, overexpression of IL-5 through pharmacological or transgenic approaches led to an increase of eosinophilic trafficking to the esophagus. Mice that were IL-5 deficient were resistant to EoE, signifying that this cytokine plays a pertinent role in the development of EoE [23]. Increased levels of IL-5 were found in the esophagus of EoE patients, whether assayed at the messenger ribonucleic acid level by real-time polymerase chain reaction or at the protein level using immunohistochemical staining [21, 34]. Antibodies targeting IL-5 were successfully used in several atopic diseases characterized by tissue eosinophilia, such as asthma [35, 36]. Similar approaches were recently attempted for EoE.

Mepolizumab

Mepolizumab is a fully humanized anti-IL-5 monoclonal antibody that has been shown to be clinically beneficial in patients with various eosinophilic diseases, such as hypereosinophilic syndrome [37] and eosinophilic asthma

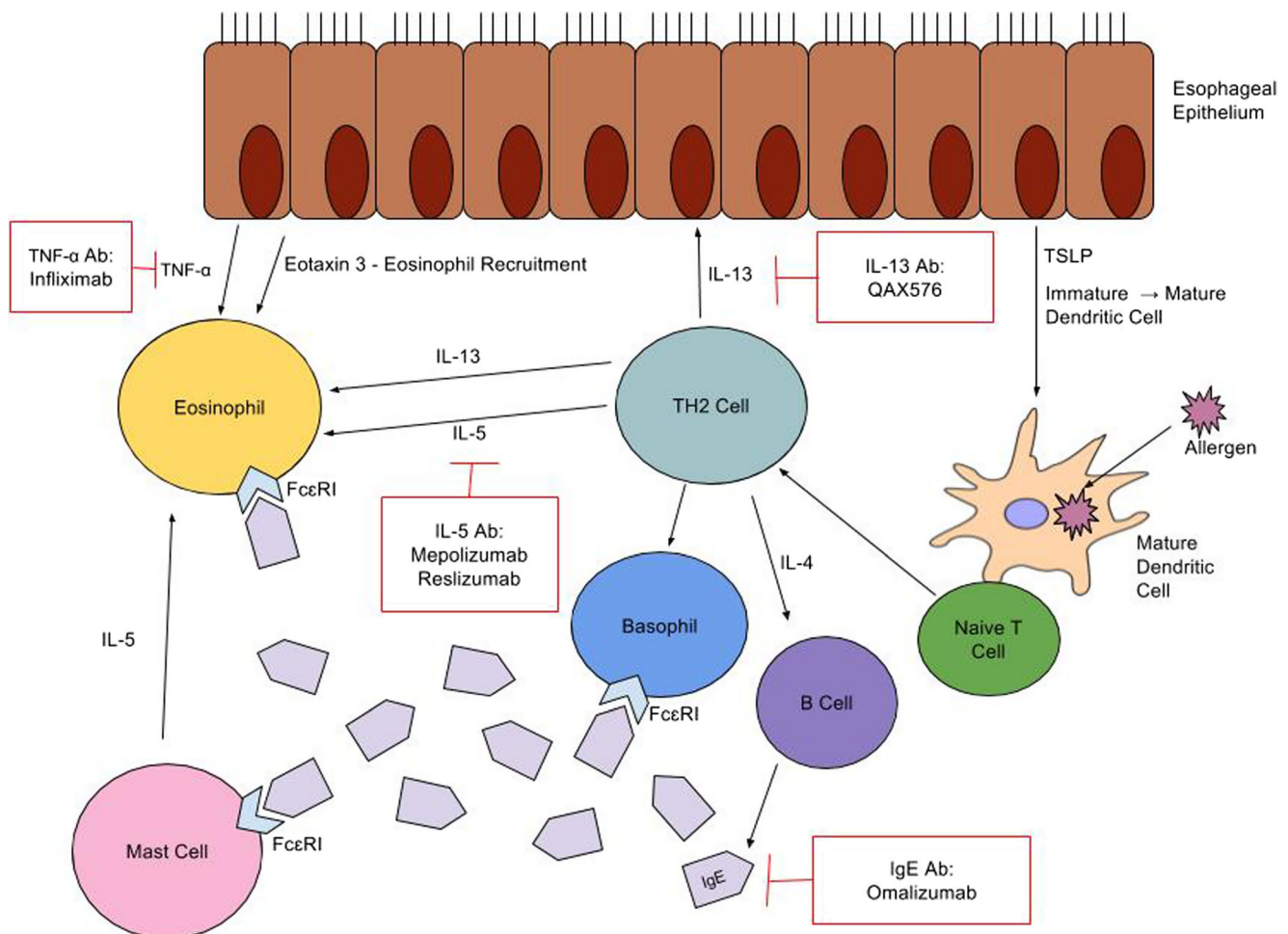


Fig. 1 Pathophysiology of eosinophilic esophagitis demonstrating targets for published biological therapies

Table 1 Summary of clinical trials using biologicals in eosinophilic esophagitis

Target	Study	Drug	Design	Population studied and size	Primary end points	Dosage	Histological response	Clinical response	Adverse effects
IL-5	Stein et al. [25]	Mepolizumab	Open-label phase I/II	Adults (n = 4)	Determine safety and efficacy of mepolizumab	Total 3 infusions of 10 mg/kg (max 750 mg)	- 8.9-fold reduction in mean esophageal eosinophils - No significant change in peak esophageal eosinophils	- Improvement of dysphagia to variable degrees - Improvement in quality of life scores, especially in the areas of physical functioning, social functioning, and self-esteem	Mainly mild, with most common symptoms being headache and upper respiratory tract infection symptoms
	Straumann et al. [26]	Mepolizumab	Randomized, double-blind, placebo-controlled	Adults (n = 11)	Histological remission (peak esophageal eosinophils < 5/HPF)	Total 2 infusions of either 750 mg mepolizumab or placebo (If histological remission was not reached, 2 more infusions of 1500 mg or placebo)	- No patients reached histological remission - 54% reduction of mean esophageal eosinophils in mepolizumab group (5% reduction in placebo group)	- Mepolizumab group had no significant improvement in clinical symptoms compared to placebo group	Well tolerated with a few mild adverse effects considered unrelated to mepolizumab
	Assa'ad et al. [27]	Mepolizumab	Randomized, double-blind, parallel-group	Children (n = 59)	Peak esophageal eosinophil count of < 5 eos/HPF	Total 3 infusions of either 0.55, 2.5, or 10 mg/kg mepolizumab (no placebo group)	- 8.8% of patients reached histological target - 89.5% reached mean esophageal eosinophils < 20/HPF - Decrease in esophageal eosinophils most marked in the 2.5 mg/kg group	- No significant changes in symptoms	Well tolerated and no related adverse effects
IgE	Spergel et al. [28]	Reslizumab	Randomized, double-blind, placebo-controlled	Children (n = 22-6)	Percent change in peak esophageal eosinophil count, and change in physician's global assessment score (EoE symptom severity)	Total 4 infusions of either 1, 2, or 3 mg/kg reslizumab or placebo	- Median reductions in peak esophageal eosinophil counts/HPF were 59%, 67%, 64% and 24% in the 1, 2, 3 mg/kg reslizumab and placebo, respectively	- Both the reslizumab and placebo groups showed improvement in the physician's EoE global assessment score, with no significant differences seen between reslizumab and placebo subjects	Well tolerated with the most common adverse effects being headache and cough
	Clayton et al. [6]	Omaliuzumab	Randomized, double-blind, placebo-controlled	Children and adults (n = 30)	Reduction in esophageal eosinophils	About 0.016 mg/kg/IgE [IU/ml] omalizumab or placebo every 2 to 4 weeks for 16 weeks	- No significant reduction in mean eosinophils/HPF compared to placebo (-1.3 and versus -4.2)	- No decrease in dysphagia score compared to placebo (-1.2 versus -1.7)	No significant adverse effects
	Loizou et al. [29]	Omaliuzumab	Open label, single arm	Children and adults (n = 24)	Effect on esophageal inflammation and symptom correlates	Omaliuzumab every 2-4 weeks based on weight and IgE level for 12 weeks	- 33% reached peak esophageal eosinophils < 15/HPF, effect more pronounced in children than adults	- Clinical remission achieved in a third of patients - 47% of patients had a significant decrease in symptoms	High drop out rate, but those that completed the trial had no symptoms

Table 1 (continued)

Target	Study	Drug	Design	Population studied and size	Primary end points	Dosage	Histological response	Clinical response	Adverse effects
TNF- α	Straumann et al. [30]	Infliximab	Open label	Adults ($n = 3$)	Effect on esophageal eosinophils	Total 2 infusions of 5 mg/kg infliximab	- No significant decrease in esophageal eosinophil counts - Proportion of responders with QAX576 40% compared to 13% with placebo (difference not statistically significant) - Mean eosinophil count decreased by 60% in the QAX576 group compared to an increase by 23.3% in the placebo group	- Symptom scores decreased in two patients but increased in the third - The difference between the two groups in the change in MDQ score was 1.8 - QAX576 group exhibited a trend towards improvement in the frequency and severity of dysphagia	serious related adverse effects Well tolerated
IL-13	Rothenberg et al. [31]	QAX576	Randomized, placebo--controlled	Adults ($n = 25$)	Proportion of responders with 75% reduction in peak esophageal eosinophils	Total 3 infusions of 6 mg/kg QAX576 or placebo			Well tolerated

[35, 36]. Mepolizumab is currently approved for use in asthmatics with peripheral eosinophilia [38]. In EoE, a few trials have been attempted.

In an open-label phase I/II safety and efficacy study [25], mepolizumab at a dose of 10 mg/kg (maximum 750 mg) was given to four adult patients with EoE, age 18–41 years. These patients had long-standing dysphagia and demonstrated a peak esophageal eosinophil count higher than 24 eosinophils/HPF from the distal or proximal esophageal mucosa. Three of those patients' disease were refractory to corticosteroid therapy, and two had an esophageal stricture. Mepolizumab was administered intravenously at weeks 8, 12, and 16. Other previously established anti-eosinophil therapies were kept during this treatment. Clinical responses and quality of life measures were determined using the short form health questionnaire SF-36, validated to assess changes in general health status in other chronic diseases [39, 40]. Endoscopic and esophageal tissue responses were determined by upper endoscopy with esophageal biopsies performed at weeks 8 and 20. Peripheral blood responses were also monitored using complete blood counts obtained every 2 weeks, serum determinations of IL-5 and eotaxin-3 levels, and the percentage of chemokine receptor type 3 (CCR3) receptors on whole blood leukocytes pre- and post-therapy. All subjects experienced improvement in clinical outcomes following mepolizumab therapy, and three of the four patients had improvements in endoscopic findings. Quality of life also improved in the four patients, with the most improvement in physical functioning, social functioning, and self-esteem. Peripheral blood eosinophilia decreased by 6.4-fold and persisted for 3 months, and the percentage of CCR3+ cells decreased 7.9-fold. Histologically, all patients had a decline in esophageal eosinophils with a mean of 8.9-fold reduction in mean esophageal eosinophils, though the peak esophageal eosinophil count remained near the threshold for diagnosing EoE (~22 eosinophils/HPF). There were no significant changes in expression levels of CCR3 receptors per eosinophil. In addition, plasma levels of IL-3 and eotaxin-3 did not correlate with the effectiveness of anti-IL-5 therapy. Adverse effects observed were mostly mild, headache and upper respiratory infection symptoms being the most common. Overall, it appeared that mepolizumab was effective in improving symptoms and overall eosinophilia, which were resistant to other therapies.

The promising results of the above study by Stein et al. led to a randomized, double-blind, placebo-controlled trial of mepolizumab in adult EoE patients [26]; the purpose of which was to evaluate the drug's efficacy to induce histological remission (peak esophageal eosinophils < 5 eos/HPF). Eleven adults with active EoE (at least one episode of dysphagia per week and peak esophageal eosinophils > 20/HPF in biopsies from either proximal or distal esophagus) participated in the study. All patients had history of inadequate response to

corticosteroids or had clinical symptom relapse with discontinuation of therapy for EoE. Gastro-esophageal reflux disease/PPI-responsive disease was ruled out in all patients by pretreatment with PPIs and negative endoscopy for signs of acid reflux disease. Patients received either intravenous infusions of 750 mg of mepolizumab or placebo twice, 1 week apart. Any concurrent other anti-eosinophil treatments were discontinued. Upper endoscopy with esophageal biopsies was performed pre-therapy and then at week 4. Those patients who did not achieve histological remission as defined above received two more infusions of either 1500 mg of mepolizumab or placebo according to their original treatment allocation, 4 weeks apart (at weeks 5 and 9). Histological assessment was done again at week 13. Patients were monitored for a total of 43 weeks. Clinical symptoms were assessed using a non-validated symptom score developed in a previous study by Straumann et al. [41], which graded frequency and severity of dysphagia. In addition, a number of immunological peripheral and tissue biomarkers of inflammation and esophageal remodeling were measured pre- and post-therapy. Clinical efficacy of mepolizumab was determined by calculating the proportion of days the subjects reported difficulty in swallowing and averaging it over the 7 days prior to the clinical visit. Histologically, although no patients reached the primary endpoint of < 5 eosinophils/HPF, esophageal eosinophil counts decreased, with a marked reduction of mean esophageal eosinophils by 54% with mepolizumab compared to 5% in the placebo group, and no further reduction with higher doses. Eosinophil numbers in the blood did not change for the placebo group but were lowered in the mepolizumab group. However, 34 weeks after the last infusion, eosinophils in the blood returned to levels seen at baseline. In contrast to the previous study mentioned, limited improvement of symptoms was seen. More than 20% clinical improvement was seen with mepolizumab between weeks 9 and 13, which increased to 30% between weeks 13 and 17 when compared to baseline. The placebo group exhibited milder improvements compared to baseline (20% between weeks 9 and 13 and 18% between weeks 13 and 17, compared to baseline). Endoscopically, 3/5 mepolizumab patients with abnormal features at baseline showed improvement, compared to 2/6 in the placebo group. Mepolizumab was well tolerated at both doses. Eotaxin-3 expression by esophageal epithelial cells did not decrease with mepolizumab therapy, but markers of esophageal remodeling (epithelial transforming growth factor- β and tenascin C) did drop with drug therapy. To conclude, although EoE remission was not achieved with this study, a significant reduction in esophageal eosinophilia and related symptoms occurred in the absence of any other concurrent therapy. It is possible that the strict study design (discontinuing concurrent therapies) or the restriction of participants to only those that were corticosteroid-refractory may have influenced the study outcome.

A pediatric study followed shortly after [27], with a similar primary outcome, which was histological, namely the proportion of patients achieving a peak esophageal eosinophil count of < 5 /HPF with 3-month therapy with mepolizumab. In a double-blind, randomized, parallel-group, prospective study, 59 children with EoE (peak esophageal eosinophils ≥ 20 eosinophils/HPF in both the distal and mid-esophagus, presence of symptoms not considered in patient selection) were selected to participate. Patients received an infusion of either 0.55, 2.5, or 10 mg/kg of mepolizumab every 4 weeks (day 0, week 4, and week 8) for a total of three infusions. Randomization was stratified by age, as two age strata, 2–7 or 8–17 years, were used. A placebo group was not present. Histological responses to therapy were assessed at weeks 12 and 24. Regarding symptom assessments, a previously developed pediatric questionnaire was used [42], which included a variety of symptoms such as abdominal and chest or throat pain, regurgitation, vomiting, and dysphagia. A total of 8.8% of the patients achieved the histological target of < 5 eosinophils/HPF. Response was similar with the three doses used, though the decrease was most marked in the 2.5-mg/kg group. A total of 31.6% of patients had peak esophageal eosinophil counts of < 20 /HPF and 89.5% had mean esophageal eosinophil counts of < 20 /HPF. The response was not sustained, as only 3.7% of the patients had a peak esophageal eosinophil count of < 5 eosinophils/HPF at week 24. Blood eosinophil counts decreased starting 24 h after treatment in all three mepolizumab groups and remained low throughout the treatment period, but returned to baseline levels after week 12. Clinically, symptoms at study entry were variable in frequency but of mild severity, and some had no reported symptoms. The younger age group had predominantly abdominal pain at study entry, while the older age group mainly complained of dysphagia. No significant change in symptoms was observed with mepolizumab therapy. It is possible, however, that the low symptom scores at study entry did not allow measurable improvement of symptoms if they were meant to occur. Regarding safety in children, the drug was overall well tolerated. In sum, this study established the safety of mepolizumab in pediatric EoE patients. Mepolizumab significantly decreased esophageal eosinophil counts but did not have a significant effect on the patients' clinical symptoms, which may in part be due to a low baseline symptom severity.

Reslizumab

Reslizumab is a humanized monoclonal neutralizing antibody to IL-5. Reslizumab prevents IL-5 from binding to the IL-5 receptor α , which is expressed by eosinophils. It has been previously shown to be effective in treating asthma [43, 44]. A double-blind, randomized, placebo-controlled study was conducted on 226 pediatric EoE patients (esophageal eosinophil count ≥ 24 eosinophils in ≥ 1

HPF from the proximal and distal esophagus, combined with at least one active gastrointestinal symptom of moderate severity or worse, and treatment with PPIs with or without histamine H₂ receptor antagonists for at least 4 weeks without symptom resolution or a normal pH probe) [28].

Patients received intravenous infusions of 1, 2, or 3 mg/kg reslizumab or placebo in a random 1:1:1:1 ratio. Randomization was stratified by atopic status. Treatments were given every 4 weeks for a total of four doses. Two co-primary outcome measures were considered in this study, percent change in the peak esophageal eosinophil count from baseline to end of therapy and change in the physician's EoE global assessment score, which was used to evaluate symptom severity. The global assessment score consisted of a semi-quantitative scoring tool for the physician to assess the subject's EoE severity, based on symptoms and physical assessment. Other outcome measures included patients' predominant symptom assessment, and the Children's Health Questionnaire, which a 50-item instrument used to evaluate the general health and well-being of pediatric patients. Median reductions in peak esophageal eosinophil counts/HPF were 59, 67, 64, and 24% in the 1, 2, 3 mg/kg reslizumab and placebo, respectively, from baseline to end of therapy. All treatment groups including the placebo group showed improvement in the physician's EoE global assessment score, with no significant differences seen between reslizumab and placebo subjects. There were no significant correlations between peak esophageal eosinophil counts and physician's EoE global assessment scores. Overall, reslizumab was well tolerated. In sum, reslizumab significantly reduced esophageal eosinophils in pediatric EoE patients compared to placebo, but improvement in symptoms was not different from placebo. It is possible that those results were limited by the non-validated method of symptom assessment for EoE, which would also explain the dichotomy between symptoms and histological findings in children with EoE, as noted in a previous study [45].

In summary, mepolizumab and reslizumab seem promising in reducing esophageal tissue and blood eosinophil counts in adults and children. However, there has yet to be a study where significant reductions in clinical symptoms occur. This could be due to the dosages or frequency of treatments, or patient selection criteria. In addition, symptom assessment was difficult in all the studies, since children present with a combination of symptoms rather than simple dysphagia, and for all ages, no validated symptom scoring tools yet exist, rendering accurate assessment of clinical responsiveness to therapy very difficult. Therefore, it may be worthwhile to re-examine some of the anti-IL-5 therapies when clinical instruments that are validated are available.

IgE

There exists a high correlation between EoE patients and atopic diseases with multiple IgE-mediated food sensitivities [46]. Increased numbers of IgE-bearing mast cells were also found in the esophagus of atopic patients with EoE [47]. Furthermore, increased density of esophageal B lymphocytes was found by Vicario et al. [48], along with upregulation of genes involved in B cell activation, class switching to IgE, and IgE production. Therefore, trials were undertaken to test whether EoE is IgE-mediated [6] and to test the efficacy of anti-IgE therapy in EoE patients [29].

Omalizumab

Omalizumab is a humanized monoclonal antibody that targets the high-affinity receptor binding site on human IgE. It is an approved treatment for moderate to severe persistent allergic asthma [49]. Besides case reports of EoE patients with concurrent food allergy treated with omalizumab [50], two clinical trials were conducted using this drug in patients with EoE. The first was a prospective, randomized, double-blind, placebo-controlled trial designed to test the hypothesis that EoE is IgE-mediated [6]. Its primary end point was histological, that of decrease in esophageal eosinophils, and the secondary end point was reduction in dysphagia symptoms. Thirty subjects were enrolled, all adults except for three subjects that were 15–17 years of age. Inclusion criteria included peak esophageal eosinophils ≥ 15 eosinophils/HPF in either proximal or distal esophagus and unresponsiveness to maximal-dose PPI. Subjects were treated with either placebo or omalizumab subcutaneously in a 1:1 ratio every 2–4 weeks for 16 weeks using a weight and serum IgE-based dosing protocol. Endoscopy with esophageal biopsies was repeated at 16 weeks. Severity of dysphagia was assessed by a semi-quantitative score, which relied to a large extent on frequency of symptoms. Compared to the placebo group, the omalizumab group had no significant reduction in mean esophageal eosinophil content and no decrease in the dysphagia score compared to placebo controls. Mast cell IgE depletion was confirmed by immunostaining after treatment with omalizumab but not in placebo-treated subjects. Serum IgE significantly increased after omalizumab treatment but not in the placebo controls, also confirming treatment effect.

The second trial was a single center, open label, single arm study, which was conducted to determine the efficacy of omalizumab in patients with EoE, 12–75 years old [29]. Although 24 patients were approached and enrolled, data on 15 subjects who completed all study procedures were analyzed. Inclusion criteria included evidence of atopy by skin or serological testing, elevated serum total IgE, peak esophageal eosinophil counts of > 15 /HPF despite PPI therapy, lack of symptom relief with dietary restriction or corticosteroids,

and presence of at least one gastrointestinal symptom. Patients received subcutaneous injections of omalizumab monthly or biweekly based on established criteria using weight and IgE level, for a total of 12 weeks. Histologically, endoscopic and histological remission (peak esophageal eosinophil count < 15/HPF) was achieved in 33% of the subjects and was more pronounced in children than in adults. Clinical remission, as assessed by a non-validated symptom score consisting of a modified version of the Crohn's Disease Activity Index, was achieved in a third of the subjects, while 47% had a significant decrease in their symptom score. Symptomatic improvement was not seen in any of the subjects who showed no histological improvement. Interestingly, EoE remission was limited to subjects with low peripheral blood absolute eosinophil counts. Esophageal mast cells were counted pre- and post-therapy, and a significant reduction was seen with omalizumab therapy, which did not correlate with the reduction in esophageal eosinophil counts. No serious adverse events were noted. The investigators concluded that in at least a subset of patients, IgE may play a role in EoE pathogenesis, and therefore may benefit from anti-IgE therapy. This study, however, was limited by its open-label design, lack of placebo controls, high drop out rate, and its *per protocol* statistical analysis.

In conclusion, although some benefit was demonstrated in the second study, its multiple study design and analysis limitations, and the lack of efficacy demonstrated in the double-blind placebo-controlled study suggest that targeting IgE may not be beneficial in treating patients with EoE.

TNF- α

An increased expression of tumor necrosis factor- α (TNF- α) has been demonstrated in the esophageal epithelium of EoE patients [21]. TNF- α can play an important immunological role in EoE, by generating a synergistic effect on IL-4 enhanced eotaxin-3 production [51], which is a highly induced, critical eosinophil-specific chemoattractant in EoE [24]. Therefore, blocking TNF- α was tested as a potential therapy for patients with EoE [30].

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody that inhibits TNF- α . Its ability to treat Crohn's disease and rheumatoid arthritis has been previously studied and has been shown to be effective [52, 53]. Straumann et al. [30] conducted a prospective study to determine the efficacy of TNF- α in decreasing esophageal eosinophilic inflammation in three adult patients with severe corticosteroid-dependent EoE. Active EoE was defined as having peak esophageal eosinophil count > 24/HPF and dysphagia with almost every meal when not on anti-inflammatory therapy. Subjects received two infusions of infliximab at 5 mg/kg at weeks 0 and 2. All concurrent

therapies were discontinued for 4 weeks prior to infliximab. Endoscopy with biopsies was performed 4 weeks following the second infliximab infusion. Symptoms were followed using a revised version of a previously published scoring system regarding esophageal symptoms [41]. Infliximab did not have a significant effect on decreasing the number of esophageal eosinophils. Endoscopic features were unchanged pre- and post-therapy. Symptom scores decreased in two patients but increased in the third one. Infliximab was well tolerated, however. Esophageal tissue expression of TNF- α decreased in two patients and was unchanged in the third one, following infliximab therapy. This study is limited by its open-label non-randomized design and small number of subjects.

Although it is possible that higher dosages of infliximab could be more effective, it seems that targeting TNF- α does not have the highest potential for treating EoE biologically due to the lack of success in both treating the eosinophilia and reducing symptoms.

IL-13

IL-13 is an important cytokine in the pathogenesis of EoE. Mishra et al. were able to induce EoE in mice through intratracheal cytokine administration of IL-13 [54]. In these experiments, no peripheral eosinophilia was elicited, suggesting that the effects of IL-13 were manifested locally in the esophagus. IL-13 messenger ribonucleic acid levels were found to be increased 16-fold in esophageal biopsy specimens of EoE patients compared to those of healthy individuals [22]. IL-13 is secreted by Th2 cells and activated eosinophils in EoE [21], and the mechanism by which it influences eosinophilia was shown to be through induction of esophageal cells to secrete eotaxin-3, which drives eosinophil chemotaxis and activation [22, 24]. Therefore, targeting IL-13 could potentially treat patients with EoE.

QAX576

QAX576 is a monoclonal antibody that inhibits the activity of human IL-13 in cell-based in vitro assays. A randomized, double-blind, placebo-controlled trial was conducted to determine the safety and efficacy of QAX576 in adult EoE patients [31]. Patients were randomly selected to either receive intravenous infusion of QAX576 (6 mg/kg) or a placebo in a 2:1 ratio every 4 weeks for a total of three doses. Repeat endoscopic and histological evaluations were done 4 weeks after the last dose. Subjects were followed up for a total of 6 months. Relapsers had the option to enter an open-label extension with three more doses of QAX576 with repeat histological evaluation. Twenty-five adult EoE patients (peak esophageal eosinophils > 24/HPF in the proximal or distal esophagus and related clinical symptoms) participated in the study. Patients were required to have PPI therapy for at least 2 months before

enrollment in order to rule out gastroesophageal reflux disease or PPI-responsive esophageal eosinophilia. Previously established baseline diets, PPIs, and nasal or inhaled steroids were kept throughout the study. The primary end point of the study was histological, consisting of proportion of responders with a 75% reduction in peak esophageal eosinophil counts compared to baseline levels in both the proximal and distal esophageal biopsies. The Mayo Dysphagia Questionnaire (MDQ) was used to assess symptoms because dysphagia is the predominant symptom found in adults with EoE. Histologically, the proportion of responders with QAX576 and placebo was 40 and 13%, respectively; the difference was not statistically significant. The eosinophil load (mean eosinophil count in the distal and proximal esophagus) decreased by 60% in the QAX576 group compared with an increase by 23.3% in the placebo group. The decrease in eosinophilia in the QAX576 was maintained for 6 months after the last dose in the majority of the QAX576-treated patients. The difference between the two groups in the change in MDQ score was 1.8. The QAX576 group exhibited a trend towards improvement in the frequency and severity of dysphagia. The drug was overall well tolerated. Reversal of esophageal eotaxin-3 gene expression was demonstrated in patients who received QAX576 using transcriptomic analysis. Overall, the primary end point of the study was not met although dysphagia severity and esophageal eosinophil counts within the QAX576 treatment group decreased, highlighting the importance of further examining anti-IL-13 antibodies in the treatment of EoE.

Summary and Conclusions

Despite the fact that none of the biologicals used so far for EoE have been highly effective, therefore none yet approved, several features are encouraging. First, this is one of the few diseases where the pediatric population received equal priority in the use of novel therapies to the adult population, as seen with the large multi-center trials with anti-IL-5 therapies. More in-depth studies will allow potential benefit for both the pediatric and adult populations as a result. Second, although most biologicals (especially those targeting the Th2 cytokines IL-5 and IL-13) showed histological benefit but no major clinical benefit comparable to placebo, one has to recognize the difficulty of evaluating symptoms in patients with EoE in the absence of validated tools. Therefore, some of these biologicals may potentially have a therapeutic role in treating EoE once clinical instruments are validated, a process currently in progress both in children and adults [55, 56]. In addition, many of these biologicals were tested in severe, steroid-refractory patients with EoE, and still demonstrated some efficacy, at least histological. Finally, the effect of the biologicals was long-lasting in the majority of the studies

discussed and had an acceptable side effect profile during the short-term studies conducted.

To conclude, although we have no biological therapies approved for EoE, the future is promising as the pathophysiology of EoE is more understood, clinical assessment methodologies are validated and tested for their responsiveness to therapy, identification of patient subsets that would respond best to biologicals are identified, and dosages and pharmacokinetics of the drugs are better studied. These biologicals are not only limited to the ones discussed above, but can include multiple others. To list a few, molecules targeting eosinophils can potentially include benralizumab, an IL-5 receptor antagonist that demonstrated efficacy in asthma [57, 58], vedolizumab, an antibody that blocks the $\alpha 4\beta 7$ integrin, which is expressed on the eosinophil surface [59], CCR3 antagonists, which also target the eosinophil surface, and Siglec8 antibodies, which also target eosinophils. Other potential biologicals targeted against molecules along the Th2 axis leading to eosinophilia can include dupilumab, an IL4/IL-13 receptor antagonist that has demonstrated efficacy in treating atopic dermatitis [60, 61] and is currently being studied in EoE (National Clinical Trial identifier NCT02379052), antibodies targeted to thymic stromal lymphopoietin, a molecule expressed in epithelial cells and capable of activating dendritic cells to prime naïve T cells to produce Th2 cytokines [62], with its gene found to be critically involved in EoE susceptibility [63], RPC4046, an antibody that binds to IL-13 $\alpha 1$ and $\alpha 2$ receptors [64] and currently being studied in EoE (National Clinical Trial identifier NCT02098473), among many other potential biologicals. Therefore, more multi-center studies are definitely needed using various biologicals to help improve the lives of children and adults with EoE.

Compliance with Ethical Standards

Conflicts of Interest Emily Ko has nothing to disclose. Mima Chehade has the following to disclose: received funding for research from Regeneron, Shire and Nutricia. Received consulting fees from Actelion, Shire and Allakos.

Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

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