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Immunotherapeutic approaches for the treatment of eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a clinical pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilia of the esophagus. When the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms, but also to prevent acute and chronic complications. The pathogenesis of EoE is most likely a mixed IgE and non-IgE food-mediated reaction, where Th2 cytokines drive esophageal eosinophilia as in other atopic diseases. Hence, it is not surprising that therapy is based on inflammation control, with steroids (oral or topical) and/or food antigen avoidance. However, these treatment options are not specific, reduce the quality of life of patients and have significant side effects, therefore, there is an ongoing effort to design more specific immunotherapies. In this review, we review standard and immunotherapeutic options for EoE treatment, such as anti-IL-5, anti-TNF α , anti-IgE, anti-CRTH, oral allergy desensitization and environmental immunotherapy.

Keywords

anti-CRTH; anti-IgE; anti-IL-5; anti-TNF α ; atopy; diet; environmental immunotherapy; eosinophilic esophagitis; oral allergy desensitization; steroids

Background

Eosinophilic esophagitis (EoE) is a clinical pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of the esophagus without pathologic eosinophilic inflammation in other parts of the gastrointestinal system [1,2]. EoE has become increasingly prevalent in the western world, with a yearly incidence now estimated to be equal to Crohn's disease [3–8]. More specifically, there has been a 70-fold increase in

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EoE incidence, from 1994 to 2011 at The Children's Hospital of Philadelphia (PA, USA; CHOP) [9] [SPERGEL J, UNPUBLISHED DATA].

EoE is suspected in patients who have symptoms related to esophageal dysfunction similar to those caused by gastroesophageal reflux (GERD) but do not improve with an optimal medical treatment for GERD. More specifically, older children and adults present with vomiting, abdominal pain, regurgitation and dysphagia and young children and infants with feeding difficulties and failure to thrive. Food impaction is a very frequent sign of EoE in adults, but is rare in infants and young children [1,9–11]. In patients with symptoms compatible with EoE it is essential to start an optimal anti-GERD therapy (in adults 20–40 mg, once or twice daily, and in children 1 mg/kg per dose once or twice daily) for 8–12 weeks (Table 1) or have a negative Ph probe before confirming the diagnosis with an esophageal-gastric and duodenal endoscopy (EGD) [2]. Because EoE clinical presentation is diverse and nonspecific, EoE diagnosis can be made only by esophageal biopsy with the finding of 15 eosinophils per high power field (eos/hpf; peak value) in one or more biopsy specimens. Such eosinophilia need to be isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically proton pump inhibitors (PPI)-responsive esophageal eosinophilia. At least four biopsies need to be obtained from multiple locations, even from areas of the esophagus, which are grossly normal, as the disease is often patchy [2].

When the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms, but also to prevent acute and chronic complications such as food impaction, esophageal stricture, narrow-caliber esophagus and esophageal perforation [2,9].

The pathogenesis of EoE is most likely a mixed IgE and non-IgE food-mediated reaction [12], where Th2-cytokines drive esophageal eosinophilia [12–22] as in other atopic diseases such as asthma and atopic dermatitis. Hence it is not surprising that therapy is based on inflammation control either with steroids (oral or topical) and/or food antigen avoidance. However, such treatment options are not specific, reduce the quality of life of patients and have significant side effects; therefore there is an ongoing effort to better understand EoE pathogenesis in order to better modulate the immune response and design more specific immunotherapies

Pathogenesis

In the last decade there has been significant progress in the understanding of EoE pathogenesis [9,12]. It is now well established that the eosinophilic inflammation typical of EoE is the expression of a Th2 inflammation driven by thymic stromal lymphopoietin (TSLP) secreted by esophageal epithelial cells [23,24] and appears to have a strong genetic predisposition (Box 1 & Figure 1) [13,23,24].

Esophageal biopsies and blood samples of patients with active EoE have increased levels of T cells, mast cells, basophils, invariant natural killer T cells and the Th2 prototypical cytokines, such as IL-5, IL-4, IL-13 and IL-15 (Box 1) [15,16,25,26]. In a mouse model that resembles EoE, mice that have been genetically modified so as to not express Th2 cytokines

or transcriptional factors essential for Th2 switching, such as Stat6, are less likely to develop disease [27]. Genome-wide association studies have found single nucleotide polymorphisms (SNPs) in TSLP and the TSLP receptor that correlate with TSLP levels and disease prevalence [13,24,28], suggesting that the Th2 inflammation could be driven locally by TSLP secreted by esophageal epithelial cells [24,28–29].

Among Th2 cytokines in a mouse model of EoE, IL-13 has been reported to play a major role with a mechanism that depends on IL-5, Stat1 and Stat6 activation [18,21]. However other studies have failed to recognize a role of IL-13 in allergen induced EoE in mice [30]. The cells responsible for such Th2 inflammation have not been completely clarified.

Eosinophils are the major infiltrating cells in EoE biopsies and are pathognomonic for EoE inflammation in the absence of GERD. However they appear to be recruited in the esophagus as a consequence of a Th2 inflammation and are not essential to maintain chronic esophageal inflammation typical of EoE. Indeed, anti-IL-5 has shown to be able to deplete eosinophils from the esophagus of EoE patients, but not to reduce symptoms or any other inflammatory manifestation in the tissue [31,32]. T cells, mast cells, invariant natural killer cells and basophils have been reported to be involved in EoE pathogenesis [15,28,33–36]. Recently, it has been shown that basophils activated by TSLP could produce Th2 cytokines and play a major role in the pathogenesis of eosinophilic esophagitis [37].

Eotaxin-3 and Rantes, which are important for Th2 cells and eosinophils recruitment, are overexpressed in EoE and there is also a strong association between a gain-of-function polymorphism in the gene that encodes Eotaxin-3 and the development of EoE in children [13,38]. Moreover eosinophils from patients with EoE express higher levels of CCR3, which is a receptor also expressed on Th2 lymphocytes and basophils, and mediates chemotaxis of these cells in response to mast cell-derived PGD₂, a key prostanoid in allergic responses [39]. Hence, specific chemokine signals could be important in EoE development (Box 1).

As in other atopic diseases such as asthma, the major long-term consequence in chronic inflammation in EoE is esophageal remodeling, which can lead to the development of irreversible strictures. Aceves and colleagues have demonstrated basal membrane thickening and increased vascular activation in untreated patients who have EoE associated with elevated TGF- β and VCAM-1 expression [40].

Other regulatory molecules, such as miRNA have been shown to play a role in EoE pathogenesis. miRNA are single-stranded RNA molecules that are very conserved during evolution and can regulate inflammation by silencing target genes [41]. Indeed, in EoE, miRNA has been implicated in the downregulation of the Th1 response, such as miR-21, mi-146a and mi146b are upregulated, and those implicated in the control of the Th2 response, such as miR-375, are downregulated. These data suggest that differences in various miRNA levels in an EoE patient could promote their Th2 inflammation [41].

In most patients, foods have been identified as the trigger of EoE Th2 inflammation with a non-IgE-mediated mechanism [9,42–44]. Some evidence suggests that aeroallergens may play a causative role in the development of EoE in humans [45]. Indeed, while the

sensitization to food allergens decreases with age, the sensitization to inhalant allergens increases with age, particularly after 4 years, [46]. Hence, there could be a stronger role for aeroallergens in adults and for food allergens in children, although no study has addressed this issue, and the literature on the role of aeroallergen in EoE remains limited.

Treatment

Current treatment is based on the use of steroids to suppress the inflammation or food allergy avoidance.

Steroids

Oral steroids, as in all atopic diseases, are very effective in quickly resolving inflammation; however, they have well-known side effects and, once suspended, the inflammation comes back unchanged [47]. Therefore, systemic corticosteroids are to be used only for emergency cases, such as severe dysphagia, hospitalization and weight loss. The long-term use of systemic steroids is not recommended [2].

Topical corticosteroids, such as swallowed fluticasone or budesonide, induce EoE remission in 50–90% of patients. Aerosolized fluticasone propionate from a metered dose inhaler ($110\text{ }\mu\text{g} \times$ two puffs, twice daily for children younger than 8 years of age; $220\text{ }\mu\text{g} \times$ two puffs, twice daily for children year older than 8 years of age) is used without a spacer [48–51]. Budesonide is delivered as viscous budesonide, which is made by mixing each 1 mg Pulmicort Respule® with 10 g (ten packets) of sucralose (Splenda™) to create a volume of approximately 8 ml [52,53]. After administration of topical steroids no food or drink is allowed for 30 min.

A study to analyze the effectiveness of nebulized versus viscous topical corticosteroid in EoE treatment demonstrated that viscous budesonide led to a significantly higher esophageal exposure to the steroid, which resulted in a lower eosinophils counts in the esophageal biopsies [54]. Moreover, topical budesonide has been shown to reverse esophageal fibrosis [55].

Limited studies have documented that, in the short-term, topical steroids are safe, except for local fungal infections (with up to 10% of patients developing oral and or esophageal candidiasis) and the possibility of mild inhibition of morning cortisol level at the highest dose (i.e., fluticasone $220\text{ }\mu\text{g} \times$ two) [SPERGEL J, UNPUBLISHED DATA] [2,52]. However, side effects in the long-term use of topical steroids remain a concern, and no study longer than 1 year has been conducted on bone health and children growth. From experience for topical steroid use in asthma it is known that moderate or high dose of topical steroids like the one used to treat EoE, are associated with significant reduction in growth in children [56,57].

Diet

Foods have been shown to be the cause of EoE through the use of targeted elimination diets, the six-food elimination diet or elemental formulas [9,42–43,58–59]. Overall, the advantages of the diet treatment compared with swallowed steroid are to achieve the

remission of the disease without using drugs. Moreover, the few children who have been reported to truly outgrow the disease were all treated with diet [9].

However, long-term elimination diets pose significant challenges to patients and families. Milk and wheat proteins generally are the most difficult allergens to remove, because they are present in the diets of the majority of children. In our clinical experience their removal may also results in the greatest nutritional impact reduce significantly the quality of life of patients and their family and pose significant health risk of malnutrition and calcium, iron, vitamin D, vitamin E and zinc deficiencies [CIANFERONI A & SPERGEL JM, UNPUBLISHED DATA] [60].

Because the current treatment is effective but has significant side effects and or reduces the quality of life of patients there is an ongoing effort to find immunotherapeutic agents that can specifically target key inflammatory molecules that are relevant for EoE inflammation.

Anti-IL-5

IL-5 is the major cytokine responsible for the differentiation, recruitment, infiltration, activation and survival of eosinophils [61]. IL-5 promotes eosinophils differentiation and activation, as well as trafficking into the lungs and esophagus [20,61]. IL-5 appears to be important in EoE pathogenesis, as It has also been demonstrated that IL-5 knockout mice are resistant to the development of EoE, whether elicited via an inhaled allergen and IL-5 transgenic mice that over-express IL-5 have elevated levels of eosinophils in the esophagus [21,62–64]. Moreover patients with EoE, by definition, have elevated numbers of esophageal eosinophils, and high esophageal tissue levels of IL-5 and IL-5 receptor (IL-5R) [25,26].

IL-5 is a homodimeric glycoprotein characterized by two identical polypeptide chains arranged in four α -helix bundles, and has a molecular weight of 40–50 kDa [65,66]. IL-5 structure is similar to the other hematopoietic cytokines, such as IL-3 and GM-CSF [65,66]. IL-5 binds to its receptor IL-5R. IL-5R α subunit is susceptible only to IL-5 binding. IL-5 binds also to the IL-5R β common (β c) signaling subunit, which also binds the cytokines IL-3 and GM-CSF [66,67]. Cells that can produce IL-5 are eosinophils, basophils, CD34+ progenitor cells, Th2 cells, mast cells, invariant NK T cells and non-B-/non-T-cell lymphocytes. IL-5R is expressed on eosinophils and basophils [66].

Blockade of IL-5 had been considered a promising target for the treatment of EoE. Hence, the two available monoclonal antibodies against IL-5 (mepolizumab [SB240563] and reslizumab [SCH55700]) have been used to target eosinophilic inflammation in EoE. Mepolizumab and reslizumab are two humanized monoclonal anti-IL-5 antibodies that have been studied in asthma treatment and have a slightly different mechanism of action. Mepolizumab blocks binding of human IL-5 to the α -chain of the IL-5 receptor complex expressed on the surface of eosinophils and other cells [68,69], whereas reslizumab is a humanized antibody that binds with high affinity to human IL-5, hence neutralizing circulating IL-5 and prevents it from binding to its receptor [69].

Spergel *et al.* studied patients who received either reslizumab or placebo in 226 pediatric patients with EoE and an esophageal biopsy specimen with randomly assigned to receive

infusions of 1, 2, or 3 mg/kg reslizumab or placebo at weeks 0, 4, 8, and 12 [32]. The studied efficacy measures were changes in peak esophageal eosinophils count (they had to have 24 or more intraepithelial eosinophils per high-power field before starting the medication) and changes in the physician's global (patients need to have symptom severity scores of moderate or worse before starting reslizumab) assessment score at end of therapy (week 15). The authors observed median reductions from baseline to the end of therapy in peak esophageal eosinophils counts of 59, 67, 64 and 24% in the 1, 2 and 3 mg/kg reslizumab (all $p < 0.001$) and placebo groups, respectively. However the physician's global assessment scores significantly improved in all treatment groups, without significant differences between the reslizumab and placebo groups. The most common adverse events in the reslizumab groups were headache, cough, nasal congestion and upper respiratory tract infection. One patient in each reslizumab group and two in the placebo group had serious adverse events; none were considered related to the study medication [32].

Similarly, in a small study of 11 adults with active EoE (>20 peak eos/hpf and dysphagia) mepolizumab significantly reduced eosinophils numbers in esophageal biopsies and improved the expression of molecules associated with esophageal remodeling. However only minimal clinical improvement was reported [70]. In this study, patients were randomized to 750 mg of mepolizumab ($n = 5$) or placebo ($n = 6$) and received two intravenous infusions, 1 week apart. Those not in complete remission (<5 peak eosinophil number/hpf) after 8 weeks received two further doses 4 weeks apart, 1500 mg of mepolizumab or placebo. A marked reduction of mean esophageal eosinophilia ($p = 0.03$) was seen in the mepolizumab group (54%) compared with the placebo group (-5%) 4 weeks after initiation of treatment. No further reduction of eosinophil numbers was observed in response to the two additional infusions in either group. Moreover mepolizumab reduced tenascin C ($p = 0.033$) and TGF- 1β ($p = 0.05$) expression in the esophageal epithelial layer 13 weeks after initiation of treatment. Clinically, limited improvement of symptoms was seen, although a trend was seen between 4 and 13 weeks after initiation of mepolizumab treatment. Mepolizumab was well tolerated. The authors concluded that mepolizumab had an acceptable safety profile, even at the high 1500 mg dose level [70].

Overall, mepolizumab and reslizumab significantly decrease eosinophils numbers in the esophageal biopsies in adults and children with EoE. However, very few patients reached normal levels and the clinical response was not different from placebo. These data confirm the importance of other cells and mediators in the pathogenesis of EoE that can be a target for immunological therapy.

Anti-TNF α

Infliximab is a chimeric IgG1 monoclonal antibody that is a potent inhibitor of TNF α . Blocking TNF α activity with infliximab has been shown to be highly effective in the treatment of several chronic inflammatory diseases, such as Crohn's disease, rheumatoid arthritis and asthma. In a single prospective pilot study, however, anti-TNF α had no benefit as a monotherapy in three male patients with severe, corticosteroid-dependent EoE, both in terms of esophageal inflammation or for symptomatic improvement [71]. The three patients received two infusions of infliximab, each containing 5 mg/kg body weight, at weeks 0 and

2. Symptoms showed a decreasing trend in patients one and three, and an increasing trend in patient 2. At baseline, two patients had severe and one patient had moderate abnormalities on endoscopy. 4 weeks after the application of the two infliximab infusions, the endoscopic abnormalities appeared almost identical to the pretreatment examination. Similarly, no significant change was noticed in the tissue eosinophilia [71].

Anti-IgE

Omalizumab is a humanized monoclonal anti-IgE antibody that binds to the IgE molecule at the high-affinity IgE receptor (FcεRI) binding site and is indicated for use in allergic asthma [72,73]. In a single study, Rocha *et al.* reported their experience on two patients with multiple food allergies and eosinophilic esophagitis on a very restrictive diet who have been treated with omalizumab (anti-IgE) in order to improve food intolerance [74]. The patients significantly improved in the reported allergy symptoms. However, no improvement was seen regarding esophageal endoscopy and histology or EoE symptoms.

Anti-CRTH

CRTH2 is a G-protein-coupled receptor highly expressed on all cells (i.e., Th2 lymphocytes, eosinophils and basophils) involved in a Th2 inflammation, such as eosinophilic esophagitis. It mediates chemotaxis of these cells to prostaglandin D2 (PGD2), a prostanoid molecule specifically produced by mast cells in allergic responses. OC000459 is a potent, selective and orally bioavailable CRTH2 antagonist, which blocks PGD2-mediated chemotaxis and activation of CRTH2-expressing cells. OC000459 has been effective in patients suffering from eosinophilic asthma [75].

In a randomized, double-blind, placebo-controlled study, 26 adult patients with severe and active EoE, which was dependent or resistant to corticosteroids, were treated either with 100 mg OC000459 (n = 14) or placebo (n = 12) twice daily. Pre- and post-treatment disease activity was assessed clinically, endoscopically, histologically and via biomarkers. After 8 weeks of OC000459 treatment, the eosinophils in the esophageal biopsies decreased significantly in the treated group and went from 114 to 73 eos/hpf, with no difference observed in the placebo group. Similarly, in the treated group, but not in the placebo one, there was a significant improvement in the physician's global assessment of disease activity. OC000459 also reduced extracellular deposits of eosinophil peroxidase and tenascin C; these effects were not seen with placebo. No serious adverse events were observed. Hence, the authors concluded that anti-CRTH2 had a modest, but significant, anti-eosinophils and beneficial clinical effects in adult patients with active, corticosteroid-dependent or corticosteroid-refractory EoE [76]. The lack of large improvement in esophageal biopsies indicated that other cells or molecules need to be blocked.

Oral allergy desensitization

Standardized oral immunotherapy (OIT) has been successfully used for treatment of IgE-mediated food allergy. In OIT the food is administered orally as the injection route has been shown to be unsafe [77]. OIT works by gradually increasing doses of allergen consumption so that the body doesn't mount an immune response against the allergen [78]. How such tolerance is achieved is still under investigation. However, during OIT, immunological

changes have been described, such as a reduction in the size of titrated skin prick tests and basophil hyporesponsiveness [79]. Moreover in some studies there has been observed a decrease in the allergen-specific IgE levels and an increase of food allergen-specific IgG4 ones and an inhibition of IgE-food allergen complex formation. These immunological changes could explain the effect of the rapid tolerance induced by OIT. Moreover, over a longer period of time (6–12 months) secretion of IL-10, IFN- γ and TNF α from peripheral blood mononuclear cells increased suggesting a shift from a Th2- to a Th1-mediated response to the allergen most likely driven by Treg expansion [79]. Dose increases of the allergen are done in a controlled setting, such as hospital or a doctor's office, whereas and daily regular ingestion of tolerated doses occurs at home [78,80]. Many uncontrolled and controlled studies have shown that a large portion of patients with IgE-mediated food allergy can be desensitized to a variety of foods, such as milk, egg, fish, fruit, peanut and celery [80–83]. A recent meta-analysis of randomized controlled trials and observational studies of oral immunotherapy in IgE-mediated cow's milk allergy patients showed that OIT, increased the likelihood of achieving full tolerance of cow's milk compared with elimination diet alone, but it had significantly more side effects such as urticaria, mild laryngospasm, mild asthma and use of oral glucocorticosteroids or intramuscular epinephrine injection. Hence the authors of the review suggested that the benefit of OIT in patients with cow's milk allergy may be counterbalanced by frequent and sometimes serious adverse effects [84].

Despite the effectiveness of OIT in the treatment for IgE mediated food allergies, one of the increasingly side effects reported by patients undergoing OIT is the development of EoE [85–88]. Sanchez-Garcia *et al.* reported three cases of EoE in 110 patients with Milk allergy treated with OIT [87]. Riodolo *et al.* reported a case of EoE due to egg in a child who had undergone a successful desensitization to egg [88]. In review of the OIT therapies and our own experience, EoE develops in 1–10% of the patients undergoing OIT, with the range varying with the food.

OIT may be inducing EoE by repeated low-dose antigenic exposure of an allergen that children are only partially tolerating. These data confirm that IgE-mediated food allergy and EoE have a different patho-genetic mechanism. This is supported by the fact that the mechanism underlying the immunologic reaction to foods in EoE is probable not IgE mediated but cell mediated. Indeed, Kelly and colleagues demonstrated that the introduction of skin test–negative foods into the diet could induce clinical disease [42]. Moreover, removal of skin test positive foods have low rate of success (13% in adults and less than 30% in pediatrics) [1,9–11,58].

In conclusion at the present time a role of OIT in the treatment of EoE has not been established or recommended at this time.

Environmental immunotherapy

Some evidence suggests that aeroallergens may play a causative role in the development of EoE in humans. A seasonal variation in cases of newly diagnosed EoE has been described, with fewer cases being diagnosed in the winter when the air contains less pollen [45]. During pollen season, there is an increased numbers of eosinophils in patient with AR compared with normal controls, although the number of eosinophils observed was lower

than values typically seen in patients who have EoE [89]. In a case report, full disease control was achieved only during non-pollen seasons [9]. The mechanism of such effect is not clear, but a recent report of treatment of EoE with environmental immunotherapy could point to a IgE-mediated mechanism. Recently De Swert *et al.* presented a case in which there was a possibility that immunotherapy to the birch pollen might have improved the symptoms and findings consistent with EoE [90]. Also Ramirez *et al.* reported a case of a child who had a EoE not responsive to diet who resolved his EoE after immunotherapy for dust mites [91].

Conclusion & future perspective

With the increase in our understanding of EoE pathogenesis, it is logical to anticipate that in the future there will be more immunotherapeutic treatment for this rapidly increasing disease. Given what we currently know of EoE pathogenesis, the next target for EoE treatment will be most likely IL-13, eotaxin or TSLP, mediators that seem to play a central role in the Th2 inflammation and be at the basis of the epithelial/immunological crosstalk.

In particular TSLP appears to be a very promising target as it is primarily secreted by epithelial cells in response to atopic cytokines (IL-4, IL-13 and TNF α) and environmental insults such as allergens and infectious agents; is a strong promoter of Th2-type allergic inflammation and it is increased in the esophageal biopsies of EoE patients [23,92–93]. Hence targeting TSLP could lead to a downregulation of the Th2 axis and may lead to potential therapeutic treatments for EoE.

Environmental immunotherapy in its current injectable form could become a viable treatment if larger studies are able to prove a role of environmental allergens in EoE pathogenesis.

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References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007; 133(4):1342–1363. [PubMed: 17919504]
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J. Allergy Clin. Immunol.* 2011; 128(1):3–20. e26. [PubMed: 21477849] [These are the most recent guidelines for the diagnosis and treatment of eosinophilic esophagitis (EoE).]
3. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin. Gastroenterol. Hepatol.* 2009; 7(10):1055–1061. [PubMed: 19577011]

4. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N. Engl. J. Med.* 2004; 351(9):940–941. [PubMed: 15329438]
5. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J. Allergy Clin. Immunol.* 2005; 115(2):418–419. [PubMed: 15696105]
6. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J. Allergy Clin. Immunol.* 2011; 128(6):1349–1350. e1345. [PubMed: 22019091]
7. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch. Dis. Child.* 2006; 91(12):1000–1004. [PubMed: 16877474]
8. Van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol. Motil.* 2012; 25(1):47–52. e5. [PubMed: 22963642]
9. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J. Pediatr. Gastroenterol. Nutr.* 2009; 48(1):30–36. [PubMed: 19172120]
10. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J. Allergy Clin. Immunol.* 2012; 130(2):461–467. e465. [PubMed: 22743304] [Addresses the effectiveness of targeted elimination diet and identifies the most common food allergen that causes EoE in children.]
11. Orenstein SR, Shalaby TM, Di Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am. J. Gastroenterol.* 2000; 95(6):1422–1430. [PubMed: 10894574]
12. Blanchard C, Wang N, Rothenberg ME. Eosinophilic esophagitis: pathogenesis, genetics, and therapy. *J. Allergy Clin. Immunol.* 2006; 118(5):1054–1059. [PubMed: 17088129]
13. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J. Clin. Invest.* 2006; 116(2):536–547. [PubMed: 16453027] [The first article to identify a genetic risk for EoE development and to extensively characterize the inflammatory mediators involved in EoE using RNA array.]
14. Gupta SK, Fitzgerald JF, Kondratyuk T, Hogenesch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* 2006; 42(1):22–26. [PubMed: 16385249]
15. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J. Allergy Clin. Immunol.* 2001; 108(6):954–961. [PubMed: 11742273]
16. Straumann A, Kristl J, Conus S, et al. Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. *Inflamm. Bowel Dis.* 2005; 11(8):720–726. [PubMed: 16043986]
17. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J. Allergy Clin. Immunol.* 2007; 120(6):1292–1300. [PubMed: 18073124]
18. Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). *Clin. Exp. Allergy.* 2005; 35(8):1096–1103. [PubMed: 16120093]
19. Blanchard C, Stucke EM, Burwinkel K, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J. Immunol.* 2010; 184(7):4033–4041. [PubMed: 20208004]
20. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J. Immunol.* 2002; 168(5):2464–2469. [PubMed: 11859139]
21. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology.* 2003; 125(5):1419–1427. [PubMed: 14598258]
22. Schmid-Grendelmeier P, Altnauer F, Fischer B, et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. *J. Immunol.* 2002; 169(2):1021–1027. [PubMed: 12097410]
23. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat. Genet.* 2010; 42(4):289–291. [PubMed: 20208534]

- 24•. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2010; 126(1):160–165. e163. [PubMed: 20620568] [Shows for the first time that thymic stromal lymphopoietin may play a central role in EoE pathogenesis, and also confirmed the importance of a genetic component in EoE development.]
25. Blanchard C, Stucke EM, Rodriguez-Jimenez B, et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2011; 127(1):208–217. [PubMed: 21211656]
26. Kinoshita Y, Furuta K, Ishimura N, Ishihara S. Elevated plasma cytokines in Japanese patients with eosinophilic esophagitis and gastroenteritis. *Digestion.* 2012; 86(3):238–243. [PubMed: 22964662]
27. Akei HS, Mishra A, Blanchard C, Rothenberg ME. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology.* 2005; 129(3):985–994. [PubMed: 16143136]
28. Siracusa MC, Saenz SA, Hill DA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. *Nature.* 2011; 477(7363):229–233. [PubMed: 21841801]
29. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat. Genet.* 42(4):289–291. [PubMed: 20208534]
30. Niranjana R, Rayapudi M, Mishra A, Dutt P, Dynda S. Pathogenesis of allergen-induced eosinophilic esophagitis is independent of interleukin (IL)-13. *Immunol. Cell Biol.* 2013; 91(6):408–415. [PubMed: 23689305]
- 31•. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut.* 2010; 59(1):21–30. [PubMed: 19828470] [The largest report in adults on the results of anti-IL-5 treatment (mepolizumab).]
- 32••. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J. Allergy Clin. Immunol.* 2012; 129(2):456–463. e451–453. [PubMed: 22206777] [The largest report in children on the results of anti-IL-5 treatment (reslizumab).]
33. Rajavelu P, Rayapudi M, Moffitt M, Mishra A. Significance of para-esophageal lymph nodes in food or aeroallergen-induced iNKT cell-mediated experimental eosinophilic esophagitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2012; 302(7):G645–G654. [PubMed: 22207581]
34. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. *J. Leukoc. Biol.* 2007; 81(4):916–924. [PubMed: 17194734]
35. Yamazaki K, Murray JA, Arora AS, et al. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. *Dig. Dis. Sci.* 2006; 51(11):1934–1941. [PubMed: 17009121]
36. Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2010; 126(1):140–149. [PubMed: 20538331]
37. Noti M, Tait-Wojno E, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat. Med.* 2013; 19(8):1005–1013. [PubMed: 23872715]
38. Blanchard C, Durual S, Estienne M, Emami S, Vasseur S, Cuber JC. Eotaxin-3/CCL26 gene expression in intestinal epithelial cells is up-regulated by interleukin-4 and interleukin-13 via the signal transducer and activator of transcription 6. *Int. J. Biochem. Cell Biol.* 2005; 37(12):2559–2573. [PubMed: 16084752]
39. Johnsson M, Bove M, Bergquist H, et al. Distinctive blood eosinophilic phenotypes and cytokine patterns in eosinophilic esophagitis, inflammatory bowel disease and airway allergy. *J. Innate Immun.* 2011; 3(6):594–604. [PubMed: 21921589]
40. Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. *Immunol. Allergy Clin. North Am.* 2009; 29(1):197–211. xiii–xiv. [PubMed: 19141355]
41. Lu TX, Rothenberg ME. Diagnostic, functional, and therapeutic roles of microRNA in allergic diseases. *J. Allergy Clin. Immunol.* 2013; 132(1):3–13. [PubMed: 23735656]

42. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995; 109(5):1503–1512. [PubMed: 7557132]
43. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2006; 4(9):1097–1102. [PubMed: 16860614]
44. Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. *Gastroenterol. Clin. North Am.* 2007; 36(1):75–91. vi. [PubMed: 17472876]
45. Wang FY, Gupta SK, Fitzgerald JF. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? *J. Clin. Gastroenterol.* 2007; 41(5): 451–453. [PubMed: 17450024]
46. Sugnanam KK, Collins JT, Smith PK, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy*. 2007; 62(11):1257–1260. [PubMed: 17711545]
47. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin. Gastroenterol. Hepatol.* 2005; 3(12):1198–1206. [PubMed: 16361045]
48. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006; 131(5): 1381–1391. [PubMed: 17101314]
49. Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2004; 2(7):568–575. [PubMed: 15224281]
50. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology*. 2002; 122(5):1216–1225. [PubMed: 11984507]
51. Caldwell JM, Blanchard C, Collins MH, et al. Glucocorticoid-regulated genes in eosinophilic esophagitis: a role for FKBP51. *J. Allergy Clin. Immunol.* 2010; 125(4):879–888. e878. [PubMed: 20371398]
52. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am. J. Gastroenterol.* 2007; 102(10):2271–2279. quiz 2280. [PubMed: 17581266]
53. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology*. 2010; 139(2):418–429. [PubMed: 20457157]
54. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012; 143(2):321–324. e321. [PubMed: 22561055] [Clinical trial showing the effectiveness of topical steroids in the treatment of EoE.]
55. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy*. 2010; 65(1):109–116. [PubMed: 19796194]
56. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N. Engl. J. Med.* 2012; 367(10):904–912. [PubMed: 22938716]
57. Turpeinen M, Pelkonen AS, Nikander K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. *Pediatr. Res.* 2010; 68(2):169–173. [PubMed: 20485203]
58. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*. 2012; 142(7):1451–1459. e1451. quiz e1414–e1455. [PubMed: 22391333]
59. Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. *Curr. Opin. Allergy Clin. Immunol.* 2007; 7(3):274–278. [PubMed: 17489048]
60. Spergel JM, Shuker M. Nutritional management of eosinophilic esophagitis. *Gastrointest. Endosc. Clin. N. Am.* 2008; 18(1):179–194. xi. [PubMed: 18061111]

61. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am. J. Respir. Crit. Care Med.* 1999; 160(3):1001–1008. [PubMed: 10471631]
62. Mishra A, Wang M, Pemmaraju VR, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology.* 2008; 134(1):204–214. [PubMed: 18166354]
63. Pope SM, Brandt EB, Mishra A, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *J. Allergy Clin. Immunol.* 2001; 108(4):594–601. [PubMed: 11590387]
64. Mishra A, Hogan SP, Brandt EB, et al. Enterocyte expression of the eotaxin and interleukin-5 transgenes induces compartmentalized dysregulation of eosinophil trafficking. *J. Biol. Chem.* 2002; 277(6):4406–4412. [PubMed: 11733500]
65. Weltman JK, Karim AS. IL-5: biology and potential therapeutic applications. *Expert. Opin. Investig. Drugs.* 2000; 9(3):491–496.
66. Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. *Clin. Exp. Allergy.* 2012; 42(5):712–737. [PubMed: 22092535]
67. Murphy JM, Young IG. IL-3, IL-5, and GM-CSF signaling: crystal structure of the human beta-common receptor. *Vitam. Horm.* 2006; 74:1–30. [PubMed: 17027509]
68. Hart TK, Cook RM, Zia-Amirhosseini P, et al. Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. *J. Allergy Clin. Immunol.* 2001; 108(2):250–257. [PubMed: 11496242]
69. Egan RW, Athwal D, Bodmer MW, et al. Effect of Sch 55700, a humanized monoclonal antibody to human interleukin-5, on eosinophilic responses and bronchial hyperreactivity. *Arzneimittelforschung.* 1999; 49(9):779–790. [PubMed: 10514907]
70. Conus S, Straumann A, Bettler E, Simon HU. Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2010; 126(1):175–177. [PubMed: 20542323]
71. Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2008; 122(2):425–427. [PubMed: 18678345]
72. McKeage K. Omalizumab: a review of its use in patients with severe persistent allergic asthma. *Drugs.* 2013; 73(11):1197–1212. [PubMed: 23812924]
73. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J. Allergy Clin. Immunol.* 2013; 132(1):101–109. [PubMed: 23810097]
74. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur. J. Pediatr.* 2011; 170(11):1471–1474. [PubMed: 21809010]
75. Barnes N, Pavord I, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin. Exp. Allergy.* 2012; 42(1): 38–48. [PubMed: 21762224]
76. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy.* 2013; 68(3):375–385. [PubMed: 23379537] [Clinical trial showing the effectiveness of CRTH2 antagonist OC000459 in the treatment of EoE in adult patients with severe and steroid resistant EoE.]
77. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol.* 1997; 99(6 Pt 1):744–751. [PubMed: 9215240]
78. Nowak-Węgrzyn A, Sampson HA. Future therapies for food allergies. *J. Allergy Clin. Immunol.* 2011; 127(3):558–573. quiz 574–555. [PubMed: 21277625]
79. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J. Allergy Clin. Immunol.* 2009; 124(2):292–300. 300, e291–297. [PubMed: 19577283]

80. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J. Allergy Clin. Immunol.* 2008; 122(6):1154–1160. [PubMed: 18951617]
81. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J. Allergy Clin. Immunol.* 2007; 119(1):199–205. [PubMed: 17208602]
82. Patriarca G, Nucera E, Pollastrini E, et al. Oral specific desensitization in food-allergic children. *Dig. Dis. Sci.* 2007; 52(7):1662–1672. [PubMed: 17245630]
83. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology.* 1998; 45(19):52–58. [PubMed: 9496487]
84. Brozek JL, Terracciano L, Hsu J, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. *Clin. Exp. Allergy.* 2012; 42(3):363–374. [PubMed: 22356141]
85. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J. Allergy Clin. Immunol.* 2009; 124(2):286–291. 291, e281–e286. [PubMed: 19477496]
86. Narisety SD, Skripak JM, Steele P, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J. Allergy Clin. Immunol.* 2009; 124(3):610–612. [PubMed: 19665770]
87. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J. Allergy Clin. Immunol.* 2012; 129(4):1155–1157. [PubMed: 22236725]
88. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann. Allergy Asthma Immunol.* 2011; 106(1):73–74. [PubMed: 21195949]
89. Onbasi K, Sin AZ, Doganavsargil B, Onder GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin. Exp. Allergy.* 2005; 35(11):1423–1431. [PubMed: 16297137]
90. De Swert L, Veereman G, Bublin M, et al. Eosinophilic gastrointestinal disease suggestive of pathogenesis-related class 10 (PR-10) protein allergy resolved after immunotherapy. *J. Allergy Clin. Immunol.* 2013; 131(2):600–602. [PubMed: 23374273]
91. Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J. Allergy Clin. Immunol.* 2013; 132(2):503–504. [PubMed: 23763975]
92. Li M, Hener P, Zhang Z, Ganti KP, Metzger D, Chambon P. Induction of thymic stromal lymphopoietin expression in keratinocytes is necessary for generating an atopic dermatitis upon application of the active vitamin D3 analogue MC903 on mouse skin. *J. Invest. Dermatol.* 2009; 129(2):498–502. [PubMed: 18650845]
93. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat. Immunol.* 2002; 3(7):673–680. [PubMed: 12055625]

Box 1. Molecules implicated in eosinophilic esophagitis pathogenesis

- Cytokines/cytokine receptors
 - IL-5, IL-4, IL-13, IL-15, TSLP, TSLP-R, TNF α
- Chemokines/chemokine receptor
 - Eotaxin-3, Rantes, CRTH2
- Cells
 - Eosinophils, basophils, T cells, B cells, mast cells and invariant NK cells
- miRNA
 - miR-21, miR-146a, miR-146b and miR-375

Executive summary

- Eosinophilic esophagitis (EoE) is a clinical–pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilia limited to the esophagus, in the absence of gastroesophageal acid reflux.
- EoE diagnosis can be made only by esophageal biopsy with the finding of 15 eos/hpf (peak value) in one or more biopsy, in the absence of gastroesophageal acid reflux.
- When EoE diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms, but also to prevent acute and chronic complications.
- The pathogenesis of EoE is most likely a mixed IgE and non-IgE food-mediated reaction, where Th2-cytokines drive esophageal eosinophilia as in other atopic diseases.
- Current treatment of EoE is based on inflammation control either with steroids (oral or topical) and/or food antigen avoidance. However, such treatment options are not specific, reduce the quality of life of patients and have significant side effects, therefore, there is a significant ongoing effort to design more specific immunotherapies.
- Anti-IL-5 treatment significantly decreases eosinophils numbers in the esophageal biopsies in adults and children with EoE. However, very few patients reached normal levels, and the clinical response was not different from placebo. These data confirm the importance of other cells and mediators in the pathogenesis of EoE that can be a target for immunological therapy.
- Anti-TNF α and Anti-IgE in small studies have shown no efficacy in treating EoE.
- Anti-CRTH has shown mild effectiveness in treating both eosinophilic inflammation and symptoms in a small group of adult patient with severe EoE resistant to steroid. Such therapy was associated with no significant side effect.
- OIT is an effective treatment of IgE-mediated food allergy, but it has not been tried in EoE yet. Indeed EoE has been reported as a side effect in children treated with OIT for IgE-mediated food allergy, confirming other clinical data that IgE-mediated food allergy does not play a central role in EoE.
- Environmental immunotherapy has been reported as an effective treatment in a couple of clinical cases. More studies are needed to understand the role of pollen and environmental allergies in EoE before environmental immunotherapy can become a mainstream treatment for EoE.

Figure 1.
Inflammation in active eosinophilic esophagitis.
GERD: Gastroesophageal reflux.

Table 1

Medical treatment of gastroesophageal reflux.

Name of drug	<10 years of age	>10 years of age	Maximum dose
Omeprazole (Prilosec®)	1 mg/kg twice a day	1 mg /kg twice a day	40 mg twice a day
Lansoprazole (Prevacid®)	1 mg/kg twice a day	1 mg /kg twice a day	60 mg daily
Esomeprazole (Nexium®)	1 mg/kg once daily	1 mg /kg once daily	40 mg daily
Rabeprazole (Aciphex®)	Not recommended	(>12 years) 20 mg once daily	20 mg once daily
Pantoprazole (Protonix®)	<40 kg body weight (limited data) 1 mg/kg once daily	>40 kg body weight 20 mg once daily	1.8 mg/kg once daily or 40 mg