Special Issue: Eosinophilic Esophagitis: From Pathophysiology To Management

Eosinophilic Esophagitis and biologics

SHORT TITLE: EoE and biologics

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All authors read and approved the final version of the manuscript.

Financial support: none

Potential competing interests: none

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Abstract

EoE incidence and prevalence have sharply increased in the last decade and management of these patients is changing rapidly. Standard regimens as elimination diet, proton pump inhibitors and topical swallowed steroids are not able to achieve remission in all patients. Moreover, loss of efficacy and safety concerns for long-term medical treatments are rising questions. As for other chronic immune-mediated diseases, biologics have been evaluated for treatment of EoE. Several targets in the Th2-mediated inflammatory cascade with eosinophilic mucosal infiltration, have been tested with alternating results. This review provides a comprehensive discussion of the available studies evaluating biologics in EoE and the possible future options most desirable for these patients.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease, characterized by symptoms related to esophageal dysfunction and, histologically, by eosinophil-predominant inflammation[12]. The incidence and prevalence of EoE have deeply increased during the last decade, especially in Western countries. Nowadays it is considered the main cause of dysphagia in young patients and the second cause of chronic esophagitis after gastro-esophageal reflux disease (GERD)[3,4]. Standard regimens as topical swallowed steroids (STC), proton pump inhibitors (PPIs) and elimination diets, are able to reach remission in most patients[5,6]. Anyway, there are some patients with severe disease that require systemic steroid treatments. Moreover, especially in the long term, it seems that PPIs and STC could lose their efficacy[7] and also patients adherence to chronic daily treatment seems to decrease over the time.

Biologics are effective and useful in many immune-mediated diseases. Starting from the better knowledge of the inflammatory cascade behind EoE pathogenesis, many molecules and cells have become possible targets to reverse esophageal eosinophilic inflammation. Borrowing information from other Th2 mediated disorders, like eosinophilic asthma and atopic dermatitis, several monoclonal antibodies have been tested in the last decade, showing swinging results.

In EoE, food and inhalator derived antigens activate epithelial and dendritic cells to produce homing and retention factors, that cause migration of immune cells[8] *(figure 1)*. These cells produce several cytokines, as IL-13, IL-4, IL-5 and thymic stromal lymphopoietin (TSLP), determining activation of Th2 cells. These, in turn, produce several cytokines that perpetuate the inflammation and trigger plasma cells to produce IgE. IL-5 acts on eosinophil precursors stimulating their differentiation, maturation and release from the bone marrow. IL-13 and IL-4 promote the transcription of calpain-14 and CCL26/eotaxin-3 genes, with the results of increasing the permeability of the epithelial membrane and further recruitment of eosinophils and mast cells[9,10]. These cells use sialic acid-binding immunoglobulin-type lectins (Siglecs), which are present on their membrane surface, to bind and interact with other immune cells[11]. In an inflammatory environment with Th2 cytokines and eotaxins, eosinophils regulate the process of epithelial-mesenchymal transition, which leads to fibrotic remodeling of the esophagus.

Biologics

Monoclonal antibodies are spreading widely in many fields of medicine, but these drugs have been tested for EoE only recently. The first report has been published in 2008, when infliximab, an antibody against the tumor necrosis factor-α (TNF-α), has been tested in three adult patients with

severe EoE. Despite TNF-α has been shown to be upregulated in esophageal biopsies from EoE patients[12], infliximab failed in inducing clinical and histological remission, after two infusions[13]. Starting from this first report, nowadays, there are many ongoing clinical trials, also in phase II and III, testing several monoclonal antibodies targeting the Th2 inflammatory cascade at various levels. They are listed below, with a brief summary of their characteristics and data available in literature *(table 1)*.

Omalizumab (anti IgE)

Presence of antigen-specific IgE is common in EoE patients[8]. Moreover, increased levels of IgE-positive cells are frequently identified in esophageal samples of active EoE[14]. From a pathophysiological point of view, this is due to the cytokinic milieu of Th2 inflammatory response, that promotes a class-switching of plasma cells with the production of IgE. Omalizumab is an anti-IgE monoclonal antibody, effective in patients with allergic asthma and chronic urticaria. It acts binding free serum IgE and preventing their interaction with mast cell and granulocyte receptors, avoiding their degranulation. Firstly, an open-label trial evaluated omalizumab in 15 EoE patients, but after 12 weeks of treatment, although tissue IgE levels significantly diminished, clinical-histologic remission was achieved only in 33% of them[14]. Subsequently, a double-blind, placebo-controlled trial of EoE adults evaluated omalizumab every 2-4 weeks for 16 weeks, based on weight and serum level of IgE. Compared to placebo, there were no differences in terms of eosinophil count nor in symptom improvement[15]. Anyway, researchers found abundant granular deposits of IgG4 on biopsies, plasma cells containing IgG4 and serum IgG4 levels reactive to specific foods, that highlighted the hypothesis that EoE is an IgG4- and not an IgE-induced allergy[15]. Moving to other eosinophilic gastrointestinal disorders (EGIDs), a 16-week open-label trial of omalizumab in 9 eosinophilic gastroenteritis (EGE) patients, showed a decrease in absolute eosinophil count, a modest trend of improvement of gastric and duodenal eosinophilic infiltration, but no significant improvement of esophageal eosinophil count[16].

Vedolizumab (anti - α4β7)

Integrin α4β7 is expressed over T lymphocytes and eosinophils[17] and helps regulating their traffic to the site of inflammation, binding the mucosal vascular addressing cell adhesion molecule 1 (MAdCAM1), expressed on endothelial cells in the intestinal tract. It is not typically expressed in the esophageal endothelium, but in vitro studies showed that MadCAM1 may be induced in the esophagus by inflammatory mediators[18]. Vedolizumab (VDZ) is an anti-α4β7 integrin monoclonal

antibody that avoids leukocytes to bind MadCAM1, causing a targeted intestinal anti-inflammatory action[19]. It also blocks αEβ7 integrin/E-cadherin axis, a marker found on Th2 cells in EoE[20]. Possible usefulness of VDZ firstly derived from two case reports of patients with EoE and Crohn's disease that experienced clinical and histologic responses after 6–12 months of therapy[21,22]. Moving to other EGIDs, VDZ has been tested in five refractory or steroid dependent EGE patients. Two of them had a clinical-histologic improvement and were able to discontinue/decrease systemic steroids. Another one had clinical improvement but did not undergo endoscopic reassessment[23]. Moreover, in another case series, ¾ of steroid-refractory EGE patients experienced a clinical and histological improvement[24].

Mepolizumab, reslizumab (anti - IL-5) and benralizumab (anti - IL-5Rα)

IL-5 plays a fundamental role in eosinophil maturation and release to the peripheric tissues, making it a perfect therapeutic target in EoE. Anti-IL-5 treatments are already effectively used in patients with severe eosinophilic asthma and nasal polyposis[25,26]. IL-5 gene appeared upregulated in esophageal samples of active EoE patients, and CD4+ T cell expression of IL-5 correlates with esophageal eosinophilia severity[27,28]. Three monoclonal antibodies have been tested against this pathway: mepolizumab and reslizumab, binding directly IL-5, and benralizumab, directed against the IL-5Rα.

Mepolizumab

Encouraging preliminary results came from a study including four adult patients with EoE non-responder to steroids and dietary modifications. After three months of therapy peak eosinophil count decreased from 153 to 28 eos/hpf, and a significant clinical improvement was reported[29]. In a subsequent randomized clinical trial (RCT), 5 patients treated with two weekly infusions of 750 mg of mepolizumab, presented a significant decrease in mean esophageal eosinophilia by 54%, even if without achieving < 5 eos/hpf (primary endpoint). Two additional infusions of 1500 mg of mepolizumab did not determine any benefit. Endoscopic findings and symptoms did not significantly improve compared to placebo[30]. Similarly, 59 children were randomized to receive mepolizumab infusions of 0.55, 2.5, or 10 mg/kg every 4 weeks. After 3 infusions, 89.5% achieved a mean eosinophil count of < 20 eos/hpf with a significant reduction in epithelial eosinophil count, but only five (8.8%) achieved a peak < 5 eos/hpf. No significant symptom improvement was reported[31]. In a case report, mepolizumab and omalizumab were used together to control symptoms in a patient with EGE and severe asthma, refractory to multiple therapies[32].

Reslizumab

Efficacy of this biologic was evaluated in children and adolescents. A RCT including two-hundred twenty-six patients evaluated reslizumab (4 i.v. infusions of 1, 2 or 3 mg/kg) every 4 weeks. In both drug and placebo groups, an improvement in global assessment scores was assessed by physicians, without statistically significant differences. Complete histological remission (< 5 eos/hpf) was achieved only in 4.4% of patients[33]. Anyway, this study was burdened by short treatment length, that could explain lack of efficacy. The open-label extension of this trial on 6 patients evaluated reslizumab efficacy and safety over a follow-up period of 9 years, demonstrating both histologic and symptomatic long-term response[34].

Benralizumab

Benralizumab blocks the IL-5 receptor on eosinophils inducing antibody-dependent cellular toxicity. Data from a subgroup of patients with hyper-eosinophilic syndrome and gastrointestinal involvement, have shown interesting results. Tissue samples from the seven patients with gastrointestinal eosinophilia, obtained at week 24, showed nearly complete depletion of eosinophils (≤ 1/hpf)[35]. A phase 3 study (MESSINA trial) evaluating benralizumab in EoE patients, is going to start soon. It will evaluate clinical, endoscopic and histologic efficacy over a 52-week treatment period (including a 24-week double-blind placebo-controlled treatment phase and a 28-week open-label treatment period) (NCT04543409). Moreover, a placebo-controlled RCT (NCT03473977) is now ongoing in eosinophilic gastritis (EG) and EGE.

QAX576 and RPC4046 (anti IL-13)

IL-13 is a key cytokine in EoE pathogenesis, which is produced by Th2 lymphocytes. It acts promoting eosinophil chemotaxis through the increase of the concentration of eotaxin-3 and it determines epithelial dysfunction, reducing gene expression of adhesion and membrane proteins[36]. Moreover, it is involved in fibrotic remodeling through the stimulation of collagen deposition[37]. Accordingly, IL-13 mRNA levels are elevated in esophageal samples from active EoE patients[37].
QAX576 and RPC4046 are two monoclonal antibodies that are being evaluated in EoE through RCTs, that block IL-13 from binding its receptor.

QAX576 (dectrekumab)

The first anti-IL-13 monoclonal antibody tested in EGIDs was QAX576[38]. In a RCT, 23 adults with EoE received QAX576 (6 mg/kg) or placebo (2:1) at weeks 0, 4, and 8, with a 6-month follow-up. Even if the primary end point was not achieved at week 12 (> 75% decrease in peak eosinophil counts) and no patient reached histological remission, the mean esophageal eosinophil count showed a reduction of 60% with QAX576 versus an increase of 23% with placebo. No significant improvement of frequency and severity of dysphagia, assessed with Mayo Dysphagia Questionnaire, was shown[38]. Indeed, subsequent trials have been discontinued.

RPC4046 (cendakimab)

Contrary to QAX576, hopeful results came from a placebo-control RCT of RPC4046, another anti IL-13 monoclonal antibody[39]. Ninety-nine active EoE adult patients randomly received RPC4046 (180 or 360 mg) or placebo (1:1:1) once a week for 16 weeks. Both RPC4046 groups showed a statistically significant reductions in mean eosinophil count compared to placebo. Also, the peak eosinophil count was significantly reduced, with half of treated patients of both RPC4046 groups having < 15 peak eos/hpf, compared with 0% placebo ($p<0.0001$). 25% of patients in the 180 mg and 20% in the 360 mg RPC4046 group had < 6 peak eos/hpf after treatment. At week 16, a significant improvement in endoscopic reference score (EREFS), histological scoring system (EoEHSS) and patient's global evaluation of disease severity was assessed. Anyway, the trend of improvement of the dysphagia symptom diary (DSD) composite score was not statistically significant. To note, in this study also patients previously refractory to topical steroids were included, showing similar encouraging response rate to RPC4046 as the non-refractory ones[39]. Recently, the 52-week, open-label, extension trial of RPC4046 has been published[40]. A year of RPC4046 treatment resulted in continuative improvement and/or maintenance of endoscopic, histologic, and clinical benefits.

Dupilumab (anti IL-4 R)

IL-4 and IL-13 are two Th2 cytokines, which have in common about 30% of their sequences. Differently from IL-13, IL-4 levels in the esophageal epithelium of patients with EoE are similar to those of healthy controls[41]. Both interleukins pathways overlap downstream, because of their binding to a common heterodimeric receptor (IL-4Rα and IL-13Rα1)[42]. For this reason, therapies directed to IL-4 and IL-13 individually could be ineffective. Dupilumab targets the IL- 4α receptor subunit, blocking the action of both interleukins. Thanks to its efficacy, it has already been approved for asthma and atopic dermatitis treatments, while ongoing trials are now evaluating dupilumab in EoE.

A phase II, double-blind, placebo-controlled RCT (NCT02379052) evaluated adult patients with moderate to severe EoE. Forty-seven patients were randomly allocated to receive dupilumab, 600-mg loading dose followed by 300 mg weekly, or placebo, for 12 weeks [43]. The primary endpoint, a significant improvement in the Straumann's Dysphagia Symptom score in treated patients at week 10, was achieved (45% vs. 19% improvement from baseline, $p < 0.05$). Moreover, considering secondary aims, 82.6% of treated patients reached a peak eosinophil count < 15 eos/hpf and 65.2% below 6 eos/hpf. Accordingly, treated patients significantly improved their EREFS and EoEHSS scores, as well as the compliance of the esophagus, measured by Endoluminal Functional Lumen Imaging Probe (endoFLIP). Dupilumab long-term efficacy and tolerability is being evaluated in an ongoing phase III RCT (NCT03633617), comparing 300 mg dose once a week or every two weeks compared to placebo, in adults and adolescents with EoE.

A phase II trial (NCT03678545) is also investigating dupilumab use in EG, with patients receiving 600 mg loading dose followed by 300 mg dose every 2 weeks, or placebo, for a period of six injections, with an optional open-label phase in the case of efficacy.

Potential Therapeutic Targets for EoE

Mechanisms behind EoE histological activity are far to be completely understood. Considering the involved inflammatory cascade, different monoclonal antibodies could act on several molecules and cells, being potentially effective in reducing eosinophilic inflammation and symptoms related to esophageal dysfunction.

Tezepelumab (anti-TSLP)

TSLP is a cytokine produced by epithelial cells, that plays an important role in many immune-mediated disorders, as inflammatory bowel disease (IBD), bronchial asthma and atopic dermatitis[36]. It is also an effective chemokine for eosinophils and resulted upregulated in patients with active EoE[44]. It acts activating antigen presenting cells, as food antigen-presenting dendritic cells in the esophageal mucosa, and promoting a TH2-weighted inflammatory response[45]. Preliminary data in murine models of EoE showed that anti-TSLP agent reduce esophageal eosinophilia and food impaction[46]. Tezepelumab (AMG 157), a fully human anti-TSLP antibody, has shown its efficacy in the treatment of adult patients with uncontrolled asthma, in a phase IIb RCT and could represent a promising option to test in EoE patients[47].

AK001 and AK002 (anti-Siglec-8)

Sialic acid-binding immunoglobulin-type lectins (Siglecs), are cell surface proteins that act on the membrane of several immune cells, playing a role in cell signaling and modulation of the immune system. Eosinophils, mast cells, and basophils preferentially express Siglec-8, that is involved in eosinophil apoptosis and clearance, inhibition of mast cell-released mediators, and reverse tissue remodeling[48]. Preliminary data from a murine model of EoE, showed that anti-Siglec-8 monoclonal antibody administration determines eosinophil reduction in esophageal, blood, and bone marrow samples[49]. Similar results were confirmed in a murine model of EGE with a significant reduction of eosinophils and mast cells in gastro-intestinal tissues, and decreased concentrations of inflammatory mediators[50]. When a monoclonal antibody binds to Siglec-8, apoptosis of activated eosinophils and inhibition of mast cell activation are induced. Clinical trials with antibodies activating Siglec 8 (AK001 and AK002) are ongoing in nasal polyposis, systemic mastocytosis and keratoconjunctivitis. A phase II RCT (ENIGMA) evaluated AK002 (1 or 3 mg/kg) vs placebo for 3 months, in adult patients with EG and/or EGE[51,52]. A 95% mean reduction of eosinophil counts in gastric and/or duodenal biopsies from baseline in treated patients has been shown. Moreover, 69% of treated patients presented a clinical and histological response, compared to 5% in placebo group. No significant differences in efficacy between low and high doses of AK002 were shown. To date, several trials are registered (NCT03664960 NCT04322708 NCT03496571 NCT04322604), in order to confirm efficacy, safety and tolerability of this biologic in EGIDs.

Discussion and conclusion

The last two decades have shown a great explosion of knowledge about EoE. In parallel, many therapeutic formulations have been tested and found effective for its treatment. The three main treatments, PPIs, swallowed topical corticosteroids and dietary regimens are able to induce a clinical and histological remission in the majority of patients. However, almost all of them are still off-label and not approved for EoE patients. Moreover, with the growing prevalence and longer follow-up periods, new therapeutic needs have born. In recent years, the idea that biologics could be useful for EoE started to be real. A position for these drugs in the therapeutic algorithm is far to be found. Translating considerations from other immuno-mediated chronic inflammatory disorders, such as IBD and asthma, biologics are useful in case of severe disease, steroid-refractory/non-responder patients, loss of response or low compliance to daily administered treatments, for steroid free maintenance therapies and in patients with several atopic comorbidities. Starting from the first possible indication, namely severe disease, even if efficacy of biologics could not be immediate, they could be of help in a combined treatment with steroids. Moving to steroid refractory patients, even if data are heterogenous[53,54], the latest studies with topical steroids showed an histological response rate

of up to 93%[6], so steroid refractoriness as indication appears to be limited to a small subgroup of patients. On the contrary, it seems that the loss of response over time could reach a significant percentage, about 50% after one and a half year[55]. Adjunctively, a multiple daily intake could determine low patient compliance. Biologics, with their longer inter-administration period, and the fact that they are performed in a medical setting for i.v. administration, could help to achieve better adherence rates. An additional consideration in favor of monoclonal antibodies is that EoE patients frequently present several atopic and immune-mediated disorders and a single agent could be effective in switch off the Th2 inflammatory pathway in all districts. So, patients with comorbidities as asthma, dermatitis and rhinitis, may discontinue multiple topic treatment and benefit from a single systemic therapy.

But not all that glitters is gold. Monoclonal antibodies present some limitations and worries related to their safety, cost-effectiveness and long-term efficacy. Although a high safety profile has been highlighted in published trials, real-world studies completely dispelling doubts related to an increased neoplastic and infective risks are still lacking. However, antibodies targeting the Th2 inflammatory pathway seem to present a favorable safety profile also in a long-term use setting, compared to other biologics[56]. Anyway, side effects and adverse events as hypersensitivity reactions, immune imbalance, overstimulation and cross-reactivity, have been reported and should be considered [57,58]. Moreover, long-term studies are required to evaluate continuative efficacy of these drugs in EGIDs. Loss of response could be related to formation of neutralizing antibodies, individual differences in bioavailability and pharmacokinetics, and increased drug clearance[59]. These problems could determine necessity to increase doses, shortening administration intervals or associations with immunosuppressants drugs[59]. Another important issue of the advent of biologics on EoE is related to a possible increase of management costs; an aspect poorly evaluated to date[60,61]. A burdening of costs is plausible, considering that a single dose of biologic could have a higher yearly cost than standard medicaments and that more medical evaluations for the administration of these drugs, clinical monitoring and endoscopic efficacy assessments could be required. It is also possible that more effective therapy with a single agent, acting in several immune-mediated diseases, could help reducing medical and social costs, especially in terms of less absenteeism and higher productivity at work[62]. Cost-effectiveness studies are indeed required to identify and set the ideal position of these drugs in the EoE management algorithm.

In conclusion, the coming years will probably see important changes in our way to manage EoE patients, thanks to the advent of biologics, able to overcome limitations of standard treatments.

Among those that are being studied, dupilumab represents the most promising one for the near future. In parallel with the blooming of trials testing new biologics, studies focused on a better knowledge of the inflammatory response and the differences among patients, are necessary to customize among available treatments offering a really effective target therapy. Moreover, cost-effective studies are required to evaluate feasibility in real-world scenario.

The possibility that these drugs could positively upset the management of EoE is not more a utopic hope, but a real chance for patients.

References.

1. 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.e6.
2. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United Eur Gastroenterol J*. 2017;5(3):335-358.
3. Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. *Gastroenterology*. 2018;154(2):319-332.e3.
4. Warners MJ, de Rooij W, van Rhijn BD, et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. *Neurogastroenterol Motil*. 2018;30(1).
5. Laserna-Mendieta EJ, Casabona S, Guagnozzi D, et al. Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. *Aliment Pharmacol Ther*. 2020;52(5):798-807.
6. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial. *Gastroenterology*. 2019;157(1):74-86.e15.
7. Greuter T, Godat A, Ringel A, et al. EFFeCtiveness AND SAFETY OF High versus low dose swallowed TopICal STEROIDs for Maintenance Treatment of Eosinophilic Esophagitis: A Multi-Center Observational Study. *Clin Gastroenterol Hepatol*. August 2020.
8. O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology*. 2018;154(2):333-345.
9. Davis BP, Stucke EM, Khorki ME, et al. Eosinophilic esophagitis–linked calpain 14 is an IL-13–induced protease that mediates esophageal epithelial barrier impairment. *JCI Insight*. 2016;1(4).
10. Cheng E, Zhang X, Wilson KS, et al. JAK-STAT6 pathway inhibitors block eotaxin-3 secretion by epithelial cells and fibroblasts from esophageal eosinophilia patients: Promising agents to improve inflammation and prevent fibrosis in EOE. *PLoS One*. 2016;11(6).
11. Legrand F, Cao Y, Wechsler JB, et al. Sialic acid–binding immunoglobulin-like lectin (Siglec) 8 in patients with eosinophilic disorders: Receptor expression and targeting using chimeric antibodies. *J Allergy Clin Immunol*. 2019;143(6):2227-2237.e10.
12. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a TH2-type allergic inflammatory response. *J Allergy Clin Immunol*. 2001;108(6):954-961.

13. Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU. Anti-TNF-α (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2008;122(2):425-427.
14. Loizou D, Enav B, Komlodi-Pasztor E, et al. A pilot study of omalizumab in eosinophilic esophagitis. *PLoS One*. 2015;10(3).
15. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014;147(3):602-609.
16. Foroughi S, Foster B, Kim NY, et al. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol*. 2007;120(3):594-601.
17. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. *J Crohn's Colitis*. 2016;10(12):1437-1444.
18. Rafiee P, Ogawa H, Heidemann J, et al. Isolation and characterization of human esophageal microvascular endothelial cells: mechanisms of inflammatory activation. Am J Physiol Gastrointest Liver Physiol. 2003 Dec;285(6):G1277-92.
19. Fedyk ER, Wyant T, Yang LL, et al. Exclusive antagonism of the α4β7 integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis*. 2012;18(11):2107-2119.
20. Lucendo AJ, López-Sánchez P. Targeted Therapies for Eosinophilic Gastrointestinal Disorders. *BioDrugs*. 2020;34(4):477-493.
21. Nhu QM, Chiao H, Moawad FJ, Bao F, Konijeti GG. The Anti-α4β7 Integrin Therapeutic Antibody for Inflammatory Bowel Disease, Vedolizumab, Ameliorates Eosinophilic Esophagitis: a Novel Clinical Observation. *Am J Gastroenterol*. 2018;113(8):1261-1263.
22. Taft TH, Mutlu EA. The Potential Role of Vedolizumab in Concomitant Eosinophilic Esophagitis and Crohn's Disease. *Clin Gastroenterol Hepatol*. 2018;16(11):1840-1841.
23. Kim HP, Reed CC, Herfarth HH, Dellon ES. Vedolizumab Treatment May Reduce Steroid Burden and Improve Histology in Patients With Eosinophilic Gastroenteritis. *Clin Gastroenterol Hepatol*. 2018;16(12):1992-1994.
24. Grandinetti T, Biedermann L, Bussmann C, Straumann A, Hruz P. Eosinophilic Gastroenteritis: Clinical Manifestation, Natural Course, and Evaluation of Treatment with Corticosteroids and Vedolizumab. *Dig Dis Sci*. 2019;64(8):2231-2241.
25. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;2017(9).
26. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *J Allergy Clin Immunol*. 2017;140(4):1024-1031.e14.

27. Molina-Infante J, Rivas MD, Hernandez-Alonso M, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Aliment Pharmacol Ther*. 2014;40(8):955-965.
28. Bullock JZ, Villanueva JM, Blanchard C, et al. Interplay of adaptive Th2 immunity with eotaxin-3/C-C chemokine receptor 3 in eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2007;45(1):22-31.
29. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006;118(6):1312-1319.
30. 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.
31. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology*. 2011;141(5):1593-1604.
32. Han D, Lee JK. Severe asthma with eosinophilic gastroenteritis effectively managed by mepolizumab and omalizumab. *Ann Allergy, Asthma Immunol*. 2018;121(6):742-743.
33. 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).
34. Markowitz JE, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and Efficacy of Reslizumab for Children and Adolescents with Eosinophilic Esophagitis Treated for 9 Years. *J Pediatr Gastroenterol Nutr*. 2018;66(6):893-897.
35. Kuang FL, Legrand F, Makiya M, et al. Benralizumab for PDGFRA-negative hypereosinophilic syndrome. *N Engl J Med*. 2019;380(14):1336-1346.
36. Arias Á, Lucendo AJ. Molecular basis and cellular mechanisms of eosinophilic esophagitis for the clinical practice. *Expert Rev Gastroenterol Hepatol*. 2019;13(2):99-117.
37. Zuo L, Fulkerson PC, Finkelman FD, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol*. 2010;185(1):660-669.
38. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2015;135(2):500-507.
39. Hirano I, Collins MH, Assouline-Dayan Y, et al. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. *Gastroenterology*. 2019;156(3):592-603.e10.

40. Dellon ES, Collins MH, Rothenberg ME, et al. Long-Term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis Q47. 2020.
41. Schmid-Grendelmeier P, Altznauer F, Fischer B, et al. Eosinophils Express Functional IL-13 in Eosinophilic Inflammatory Diseases. *J Immunol*. 2002;169(2):1021-1027.
42. Vatrella A, Fabozzi I, Calabrese C, Maselli R, Pelaia G. Dupilumab: A novel treatment for asthma. *J Asthma Allergy*. 2014;7:123-130.
43. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis. *Gastroenterology*. 2020;158(1):111-122.e10.
44. Travers J, Rochman M, Miracle CE, Cohen JP, Rothenberg ME. Linking impaired skin barrier function to esophageal allergic inflammation via IL-33. *J Allergy Clin Immunol*. 2016;138(5):1381-1383.
45. de Rooij WE, Dellon ES, Parker CE, et al. Pharmacotherapies for the Treatment of Eosinophilic Esophagitis: State of the Art Review. *Drugs*. 2019;79(13):1419-1434.
46. Noti M, Wojno EDT, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med*. 2013;19(8):1005-1013.
47. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.
48. Kiwamoto T, Kawasaki N, Paulson JC, Bochner BS. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. *Pharmacol Ther*. 2012;135(3):327-336.
49. Rubinstein E, Cho JY, Rosenthal P, et al. Siglec-F Inhibition Reduces Esophageal Eosinophilia and Angiogenesis in a Mouse Model of Eosinophilic Esophagitis. *J Pediatr Gastroenterol Nutr*. 2011;53(4):409-416.
50. Youngblood BA, Brock EC, Leung J, et al. Siglec-8 antibody reduces eosinophils and mast cells in a transgenic mouse model of eosinophilic gastroenteritis. *JCI Insight*. 2019;4(19).
51. Dellon E, Peterson K, Murray J, Flak G, Efficacy and safety of AK002 in adult patients with active eosinophilic gastritis and/or gastroenteritis: primary results from a randomized, double-blind. J NG-UEG, 2019 undefined.
52. Lucendo AJ, López-Sánchez P. Targeted Therapies for Eosinophilic Gastrointestinal Disorders. *BioDrugs*. 2020;34(4):477-493.
53. 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.e1.
54. Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis.

55. Eluri S, Runge TM, Hansen J, et al. Diminishing Effectiveness of Long-Term Maintenance Topical Steroid Therapy in PPI Non-Responsive Eosinophilic Esophagitis. *Clin Transl Gastroenterol*. 2017;8(6):e97.
56. Aubin F, Carbonnel F, Wendling D. The complexity of adverse side-effects to biological agents. *J Crohn's Colitis*. 2013;7(4):257-262.
57. Aranez V, Ambrus J. Immunologic Adverse Effects of Biologics for the Treatment of Atopy. *Clin Rev Allergy Immunol*. 2020;59(2):220-230.
58. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2019;199(4):433-445.
59. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*. 2016;7(1):e135.
60. Mukkada V, Falk GW, Eichinger CS, King D, Todorova L, Shaheen NJ. Health-Related Quality of Life and Costs Associated With Eosinophilic Esophagitis: A Systematic Review. *Clin Gastroenterol Hepatol*. 2018;16(4):495-503.e8.
61. Dellon ES. Cost-effective care in eosinophilic esophagitis. *Ann Allergy, Asthma Immunol*. 2019;123(2):166-172.
62. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. *Am J Gastroenterol*. 2015;110(5):626-632.

Figure 1. Mechanisms of Eosinophilic Esophagitis pathogenesis and therapeutic targets

Table 1. Biologics acting on Eosinophilic Esophagitis

Monoclonal antibodies	Pharmacological targets	Related references
Infliximab	TNF-α	13
Omalizumab	IgE	14,15,16,32
Vedolizumab	α4β7	21,22,23,24
Mepolizumab	IL-5	29,30,31,32
Reslizumab	IL-5	33,34
Benralizumab	IL-5Rα	35, NCT04543409, NCT03473977
QAX576	IL-13	38
RPC4046	IL-13	39,40
Dupilumab	IL-4R	43, NCT02379052
Tezepelumab	TSLP	46
AK001	Siglec-8	49,50
AK002	Siglec-8	49,50,51,52, NCT 03664960, NCT04322708, NCT03496571, NCT04322604

TNF: tumor necrosis factor; IgE: Immunoglobulin E; IL: Interleukin; TSLP: Thymic Stromal LymPhopoietin; Siglec: Sialic acid-binding immunoglobulin-type lectin