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# Pharmacological treatments for eosinophilic esophagitis: current options and emerging therapies

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**Running title:** Pharmacological treatments for eosinophilic esophagitis

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**Abstract**

**Introduction**: The epidemiology of eosinophilic esophagitis (EoE) has increased rapidly to represent a common cause of chronic and recurrent esophageal symptoms. Current treatment options have limitations so the development of novel therapies is a matter of growing interest.

**Areas covered**: This article provides an up-to-date discussion of current therapies and investigational options for EoE. Established anti-inflammatory treatments for EoE at present include dietary therapy, proton pump inhibitors and swallowed topic steroids, which should be combined with endoscopic dilation in case of strictures. Refractoriness, high recurrence rates and need for long-term therapies has promoted the investigation of novel, esophageal-targeted formulas of topic corticosteroids, and monoclonal antibodies (including mepolizumab, reslizumab, QAX576, RPC4046, dupilumab, omalizumab, infliximab and vedolizumab) for EoE, with some having been demonstrated as effective and safe in the short term. Several additional promising therapies are also discussed.

**Expert opinion**: Several therapeutic targets have shown efficacy and will be approved to treat EoE, especially corticosteroid-sparing options and those for patients with multiple Th2-associated diseases. Personalized therapeutic strategies for initial and maintenance treatments of EoE must be rationally designed, to reduce the burden of disease and answer meaningfully the needs of all stakeholders involved in EoE.

**Key words:** Eosinophilic esophagitis (EoE); mepolizumab; reslizumab; dupilumab; swallowed corticosteroids; budesonide; fluticasone; food-elimination diet; proton pump inhibitor (PPI); biological therapy

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**Article Highlights**

- Therapeutic goals in EoE are evolving from the mere control of symptoms and eosinophilic inflammation, to reversing and preventing fibrotic complications, guaranteeing nutritional status, and restoring or maintaining social relationships and quality of life.
- Current EoE treatments include diets that eliminate disease-triggering foods, PPIs and various swallowed topical corticosteroid formulations, as well as endoscopic dilation in cases of reduced-gauge esophagus. Used appropriately they constitute an effective treatment to achieve and maintain the remission of EoE in a significant proportion of patients.
- Novel formulations of topic corticosteroids targeted to the esophageal mucosa are showing high rates of histological remission, both as inductions for maintenance therapy, and potentially allowing for small dose usage. Despite topic corticosteroids appearing to be safe in the long term, patient relapse is common when administration is stopped.
- New drugs under development, especially monoclonal antibodies, are being proposed to overcome the unmet medical needs of current EoE patients. Most are imported from other Th2-mediated allergic diseases and are being suggested as potentially having modifying effects on the natural history of the disease, however, this is yet to be demonstrated.
- After the failure of the anti-IgE antibody omalizumab and IL-5 blockers mepolizumab and reslizumab, anti-IL-13 drugs show some effectiveness. The IL-4 receptor antagonist dupilumab is the most promising option on the horizon, but several molecules acting over different points at the intimate mechanisms leading to EoE are also potential therapies.
- The availability of novel therapies for EoE will require re-designing rational and realistic strategies for initial and maintenance treatment of EoE, including patient-centred approaches and shared decision-making models. The goal is to overcome the limitations of current options while trying to answer meaningfully the needs of all stakeholders involved in EoE.

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## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-driven inflammatory disease characterized by dense eosinophilic infiltration restricted to the esophageal mucosa that typically presents with symptoms of esophageal dysfunction [1]. The prevalence of EoE has sharply increased during the last decade, especially in Western countries [2], to the point that it is recognized today as the leading cause of dysphagia and food impaction among children and young adults, and as the second cause of chronic esophagitis after gastroesophageal reflux disease (GERD) [3]. Left untreated, symptoms and inflammation in EoE tend to persist [4]; after treatment cessation, clinical relapse is usual [5]. In the majority of cases, the natural course of the disease appears to be progressive, leading to esophageal remodeling with stricture formation and functional damage in the long term [6-8]. The chronic and progressive nature of EoE and its recurrent symptoms impact on health-related quality of life (QoL) [9] and clearly indicates a need to treat symptomatic patients. In fact, improving symptoms and QoL are identified by patients as the most relevant therapeutic targets in EoE [10].

Almost 3 decades after first being characterized as a distinctive disorder [11,12], research on the causes of EoE and its treatment has increased exponentially [13]. However, large-scale epidemiological studies to define potential risk factors are still needed and the ideal regimen to treat patients with EoE remains undefined. The unmet needs of patients with EoE have been recognized by pharmaceutical and biotechnological companies, which are currently allocating resources to the potentially expansive market of diagnosis and therapy of EoE.

As EoE constitutes a particular food allergy triggered predominantly by food antigens [14], several modalities of dietary therapy used to target the primary cause of the disease have been shown to be effective in inducing [15] and maintaining disease remission [16]. Multiple trials and meta-analyses have shown swallowed topic corticosteroids as effective in inducing histological remission of the disease [17-19]; novel esophagus-targeted formulations also achieve symptoms improvement [20,21]. Proton pump inhibitors (PPIs) are an anti-inflammatory therapy [22] able to achieve [23] and maintain [24-26] histological and symptomatic remission in 50% of patients. Finally, esophageal dilation provides symptom relief in up to 95% of patients [27] and should be considered in cases with esophageal strictures or narrow caliber esophagi and persistent dysphagia/food impaction, despite effective anti-inflammatory treatment [28].



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A structured and evidence-based framework for treating patients with EoE has been provided over the last decade through several consensus documents and clinical practice guidelines [1,29-31]. However, there is still a high proportion of patients unable to have their disease controlled with current therapeutic options, and substantial variations in adherence to guidelines regarding treatment choice and assessment of response have been documented [32-36], which limits assessing the effectiveness of the different interventions available for EoE.

This article summarizes the efficacy of current pharmacological strategies for treating patients with EoE and discuses the shortcomings of the available treatment approaches. Novel pharmacologic alternatives, potential therapeutic targets currently under investigation and others on the horizon are also presented.

## 2. Goals of Therapy in EoE, Limitations for Assessment of Effectiveness

Just as with other chronic inflammatory diseases such as inflammatory bowel disease (IBD), the goals of therapy in EoE have changed with the increase in knowledge [37]. Treatment endpoints in both diseases have evolved from mere symptomatic improvement towards, ideally, the complete resolution of symptoms, histological inflammation and endoscopic findings (mucosal healing), and to preventing remodeling and related complications [38,39]. Current therapeutic targets in EoE should now include maintaining a proper nutritional status while avoiding macro and micro-nutrient deficiencies, correcting feeding dysfunction, restoring social activities and increasing QoL [40,41]. Avoiding drug side effects and long term diets is a further goal.

However, the lack of validated definitions for symptomatic, endoscopic and histological remission constitutes a major challenge in EoE therapy. At present, no consensus exists on histological remission, having been defined by several trials as variable degrees of reduction in peak eosinophil counts. A peak eosinophil count below the diagnostic threshold of 15 eosinophils per high power field (eos/hpf) seems to be appropriate to identify most patients with symptom and endoscopic improvements in regular clinical practice [42], but stringent histological thresholds <6 eos/hpf are defined in most trials assessing drugs for EoE, as also suggested by the Food and Drugs Administration. Additional histological findings accompanying eosinophilic infiltration are assessed through the EoE Histology Scoring System [43]: this evaluates 8 individual histologic features and potentially overcomes the limitations of assessing eosinophil counts alone [44]. Its potential advantages over simply counting cells are being assessed by a number of randomized controlled trials (RCT) [45].



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As for symptoms, the lack of dysphagia or food impaction episodes does not necessarily involve disease remission: patients suffering longstanding dysphagia often develop adapting behaviors to cope with symptoms or facilitate the passage of food. These include prolonged eating time, modification of food texture by lubrication with water or sauces, avoiding highly solid foods or restricting social activities, which frequently are not captured by generic instruments used to assess dysphagia [46,47]. Disease-specific novel instruments overcome these limitations by assessing not only the symptoms, but also quantifying the difficulties foreseen by patients in eating different food consistencies and dietary or behavioral modifications for specific foods [48-50]. These instruments are being used in trials but are not yet incorporated in the real-world practice [51].

Ideally, current therapeutic goals in common clinical practice would be complete symptom resolution and normalization of the esophageal epithelium with elimination of all eosinophils, but in practice, symptom improvement and histological response do not always correlate. In fact, symptoms cannot accurately predict remission in EoE, and the use of validated instruments does not overcome this limitation [52,53]. Although medical therapy can achieve histological remission of EoE, this may not be sufficient for esophageal strictures. Therefore, the improvement or resolution of endoscopic findings has appeared as an increasingly relevant goal in clinical trials in EoE, evaluable from the EREFS scoring system which grades the five major esophageal endoscopic features in this disease (edema, rings, exudates, furrows and strictures) [54]. The improvement of inflammatory and especially, the fibrotic features, is now included among the objectives of any EoE treatment, with an endoscopic remission criterion still to be agreed.

## 3. Therapeutic Algorithm and Current pharmacologic therapies for EoE

The proposed therapeutic algorithm for EoE is summarized in **FIGURE 1**. PPIs, diet, or topical steroids might be offered as first line anti-inflammatory therapy. The choice of therapy should be individually discussed with the patient and might be potentially interchangeable over time. The efficacy of any therapy should be checked by a follow-up endoscopy after a 6- to 12-week initial course. In responders to any empiric 6-week diet, all food groups are reintroduced individually, with an endoscopy performed following each food challenge. The final goal is to provide a personalized maintenance therapy, with long-term removal solely of food triggers, namely, foods proven to induce esophageal inflammation after individual reintroduction. In cases of unresponsiveness, a choice between other drugs and dietary therapy should be made. Once an effective



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therapy is instigated, disease remission should be maintained using the same option, however, this might be changed over time if there are treatment side effects or the patient is unwilling to continue with medication (PPIs or topic steroids) or there is a negative impact on quality of life and family resources (dietary restrictions) [1]. Uncertainties not resolved by the current EoE algorithm include the optimal dose of topic steroids in the maintenance phase and methods and frequency of patient follow-up.

### *3.1. Proton pump inhibitors*

The role of PPIs in EoE management has been one of the most changing aspects throughout the short life of the disease, and over the course of just a decade they have gone from being an instrument to rule out GERD as a cause of esophageal eosinophilia [29], to the defining factor of a new clinical entity as a differential diagnosis of EoE (the so-called PPI-responsive esophageal eosinophilia) [30] and, finally, to constitute a true anti-inflammatory treatment for EoE [1].

Despite the complex relationship between EoE and GERD established through the bidirectional hypothesis that the dysmotility associated with EoE would favor poor acid clearance [55,56], or that acid exposure damages the esophageal mucosa and increases the permeability of the epithelial mucosal barrier thus favoring the uptake of antigens from the esophageal lumen [57], several studies have repeatedly documented the ability of PPIs to reduce both symptoms and eosinophilic infiltration in patients of all ages. In fact, the acid-independent anti-inflammatory properties of PPIs were first demonstrated in EoE: PPI therapy significantly downregulated esophageal gene expression of eotaxin-3/CCL26 and T helper (Th)2 cytokines interleukin (IL)-5 and IL-3 in biopsies from patients with EoE, similarly seen in patients treated with topic steroids [58].

The first evidence on the potential utility of PPIs to achieve both clinical and histological remission of EoE was provided in the early pediatric literature [59-61]. Subsequently, several clinical trials and prospective studies showed that PPI therapy is able to induce histological remission of the disease (defined as a reduction of eosinophilic infiltrate below 15 eos/hpf) in 47% to 57% of patients of all ages [25,62,63]. A systematic review with meta-analysis, including 33 studies involving 619 patients with EoE, showed that PPIs led to histological remission (defined as <15 eos/hpf) in 50.5% (95% CI: 42.2-58.7%) and symptomatic improvement in 60.8% (95% CI: 48.38-72.2%), without differences irrespective of patient age, study design or type of PPI evaluated. However, a trend towards greater efficacy was observed when the daily dose was divided into



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two, and among patients with pathological GERD at pH monitoring (23). Recommended PPI doses in adults are omeprazole 20-40 mg twice daily or equivalent; in children, 1-2 mg/kg of omeprazole daily or equivalent. In EoE patients with an initial response to PPI therapy, this drug should be used also to maintain disease remission in the long term, because discontinuation of therapy leads to symptomatic and/or histological relapse. The long-term strategy is to use the minimal effective dose to maintain remission. A prospective series in children showed that 78% of them remained in remission after one year with half the dose used for induction [25]. In adults, PPIs at half the initial dose maintain clinical and histological remission in at least 75% of patients after at least 1 year of follow-up [24,26]. Most relapsing patients recover remission after dose escalation. There is no published data on PPI safety concerns in patients with EoE.

### *3.2. Topic coticosteroids*

From the initial descriptions of EoE, topically administered corticosteroids with reduced bioavailability (fluticasone propionate and beclomethasone), swallowed instead of inhaled, proved to be effective in inducing clinical and histological remission in a short series of four children with EoE [64]. Later on, topic swallowed corticosteroids were shown to have the same effectiveness as oral prednisone in inducing clinical and histological remission of EoE in a 4-week RCT [65]. Since systemic corticosteroids present no advantages in terms of symptom resolution, relapse rates, or time to relapse, and have significantly more severe adverse effects, they have been replaced by topic corticosteroids to treat EoE. Systemic steroids are not generally recommended in EoE [1], and their use is restricted to emergency situations with severe dysphagia or significant weight loss.

Four systematic reviews with meta-analyses released in recent years have summarized evidence from a number of RCTs on the efficacy of topic corticosteroids compared to placebo in inducing remission of EoE [17-19,66] and one more has compared its effectiveness with that of PPIs [67]. Even though histological remission was defined differently in most of the studies, with (slightly) different cut-offs applied for the number of eosinophils, both budesonide and fluticasone propionate were shown to be significantly superior to placebo in reducing peak eosinophil densities below the diagnostic threshold of 15 cells/hpf (OR 24.6; 95% CI 7, 86.8) [18] and in achieving complete histological response (OR 14.8; 95% CI 3.2, 69.2) [19]. The histological response however was not accompanied by a uniform and convincing remission of symptoms in all cases, mainly due to the use of non-structured or un-validated



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instruments in several trials. For example, one systematic review shown budesonide as significantly superior to placebo in terms of symptomatic relief (OR 7.20; 95% CI 2.15, 24.05) but not fluticasone propionate (OR 1.27; 95% CI 0.44, 3.65) [19]. The several doses assessed in the different RCTs, but specifically the different drug administration methods used to deliver the topic steroid inside the esophageal lumen, explain the differences in the effectiveness of fluticasone propionate and budesonide to target EoE.

Topical corticosteroids used to treat EoE are marketed for use in asthma or rhinitis, in the form of multi-dose inhalers, nasal drops or aqueous nebulizer solutions. Patients should swallow its content to coat the esophageal mucosa with the medication. Fluticasone or budesonide have shown comparable potencies, but the vehicle to deposit the drug on the inner surface of the esophagus is essential: A RCT that compared two formulations of budesonide (oral and nebulized viscose) administered at the same doses showed that oral viscose budesonide provided a higher level of esophageal coverage due to a longer contact time between the mucosa and the medication, which resulted in greater reduction of esophageal eosinophil counts and endoscopic normalization [68].

Recently, a budesonide orodispersible tablet (BOT) formulation, that provided an efficacy of almost 100% in achieving histological remission after 2 to 6 weeks of therapy, has been approved as the first drug to treat EoE in adult patients and, after being approved by the European Medicines Agency, it is already available in several European countries [21]. The efficacy and safety of several doses of APT-1011, an orally disintegrating tablet formulation of fluticasone propionate, are being currently compared to placebo in a RCT, for an initial 12-week treatment period followed by an additional 40-week maintenance phase in adults with EoE (ClinicalTrials.gov Identifier NCT03191864). Dose ranges and specific instructions for administration of topic steroids in EoE are presented in **TABLE 1**.

In contrast, evidence of the effectiveness of topic corticosteroids to maintain remission of EoE over the long term is scarcer. A RCT found low-dose budesonide to be more effective than placebo in maintaining EoE in histological and clinical remission in adults [69]. As for children, the extension of a RCT assessing high-dose fluticasone (1760 mcg/day) demonstrated a sustained remission in 73% of initial responders who then went to a 50% dose reduction when re-evaluated 3 months later [70]. Results of the one-year maintenance therapy with BOT after induction of remission have been recently reported [69]: EoE maintained clinic-histological remission in 74.3% of patients



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treated with budesonide but only in 4.4% of patients treated with placebo. No significant difference was found for 1 mg BID or 0.5 mg BID budesonide doses. In patients treated with placebo the median time to clinical relapse was 87 days. Such data supports the recommendation to continue with topical corticosteroids in those initially steroid-responsive patients in order to maintain remission.

The safety profile of swallowed topical corticosteroids seems to be favorable, since no serious side effects have been reported. However, esophageal candidiasis has been described in up to 10% of patients of all ages treated with several compounds. Most of these cases were incidental findings during scheduled endoscopies, and easily resolved after specific treatment with no need to withdraw steroid therapy.

Used in the long term, topic corticosteroids did not increase rates of candidiasis [71]. The possibility of suppressing systemic cortisol by topic corticosteroids has recently arisen, especially in children. Despite urine and/or serum cortisol levels being not suppressed in children [70] or adults [21,46,72] in short and long term [69,71] RCTs, concerns over long-term effects of swallowed topical steroids on adrenal suppression in children are being provided by short series of EoE patients. Results are conflicting due to different methods of defining adrenal suppression and determining adrenal function (basal cortisol levels, low dose ACTH stimulation test, or standard dose ACTH stimulation test) and differences in times of measuring cortisol levels after ACTH stimulation dose [73-76]. The minority of cases for adrenal insufficiency came from uncontrolled observational studies [77] and so far, no clinical signs of adrenal insufficiency or growth impairment have been reported. Pending further data, the current advice is to control cortisol levels in children with EoE to prevent adrenal insufficiency, especially if they swallow high doses of corticosteroids for prolonged periods, or if they also use inhaled/nasal corticosteroids to treat concomitant atopies [1].

***Unmet medical needs and potential improvements in EoE therapy***

Current diets and drug-based therapies certainly allow remission of esophageal inflammation and symptoms to be achieved and maintained in a high proportion of patients with EoE. However, diet, PPIs and topic steroid-based options have not been shown to be effective disease-modifying treatments, as the recurrence of symptoms and inflammation after treatment discontinuation is common. In addition, some concerns regarding the use of current treatment approaches have emerged. To begin with, no allergy test is available to correctly identify food trigger(s) of EoE so patients should empirically exclude several foods one at a time; the empirical elimination of the



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6 foods most commonly associated with food allergy from patients' diets leads to disease remission in up to 3/4 parts of patients. Despite being highly restrictive, it allowed to identify the frequencies with which each food is involved in the origin of the EoE, by sequential reintroduction under endoscopic monitoring with biopsies. This have resulted in less restrictive empirical diets, such as those that exclude 4 and 2 foods [78]. However, dietary therapies are not a panacea and ~25% of patients will never respond to empirical elimination diets [16]. Endoscopy with biopsies is the only accurate method to verify disease remission after 6 weeks of food elimination and the low reliability of symptoms to predict inflammatory activity after food reintroduction [52] also requires endoscopy to identify food triggers for EoE. Long-term adherence to the diet is required since there is no evidence that patients will outgrow their EoE food trigger. The long term feasibility of a diet for EoE greatly depends on the number of culprit foods and a single food will be the cause of EoE in less than half of patients overall [78]. The fact that milk, wheat, egg or soy/legumes are the foods that cause EoE more frequently and their wide distribution in staple diets restricts this treatment option to the most motivated patients.

PPI therapy is generally considered safe although there have been recent concerns on the potential complications with long-term use [79,80]. They are used off-label in EoE and one quarter of the patients who respond to double doses will need this high dose to maintain sustained remission in the long term [24]. Swallowed topic corticosteroids are effective and appear safe, even in the long term. However, patients frequently relapse when corticosteroids are stopped because they do not modify the natural history of the disease [5]. Newly released formulations for budesonide designed to coat the esophageal mucosa have improved the results of previous slurry formulations or inhaler devices, but still a small proportion of patients are non-responsive [81].

All these facts, together with the growing epidemiology of EoE, have generated an enormous interest in the pharmaceutical industry for the development of new drugs, to respond to unmet medical needs of current EoE patients. They consist mainly of monoclonal antibodies, most of them imported from other Th2-mediated allergic diseases, which have been proposed as being potentially effective in EoE also, with a possible modifying effect on the natural history of the disease that is yet to be demonstrated.

## 4. Monoclonal antibodies

Biologic agents have become an essential therapeutic option for a variety of intestinal, skin and articular inflammatory diseases, autoimmune conditions, and malignancies. In



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recent years they have also expanded to atopy, especially allergic and eosinophilic airway inflammation, common to most asthma patients [82]. Their use in EoE started as early as in 2008: Infliximab, a monoclonal antibody directed toward Th1 cytokines failed in inducing EoE remission in a short series of adult patients [83]. The involvement of a Th2-mediated response in EoE [84], in which interleukin (IL)-4, IL-5 and IL-13 play a central role, allowed the assay of further biologic drugs.

The pathophysiology of multiple allergic processes involves the production of antigen-specific IgE as a central component, which is promoted by a Th2-mediated class-switching of plasma cells. As an evidence of an immediate hypersensitivity in EoE, patients usually show high levels of total and food-specific serum IgE, as well a positive results in allergen-specific skin tests (SPT) [85]. As also seen in other IgE-mediated allergic conditions, such as bronchial asthma [86] and allergic rhinitis [87], the inflammatory infiltration of EoE includes dendritic cells, mast cells and B cells [88,89] which are able to class switch and generate IgE locally [89]. Therefore, omalizumab, an anti-IgE monoclonal antibody effective in controlling severely allergic asthmatic patients, was also assessed as a treatment for EoE on 30 adult patients who were randomized to receive either omalizumab or placebo in a double-blind RCT [90]: Eosinophil counts were not altered in in biopsy samples of patients treated with omalizumab, nor did they improve symptoms compared to placebo. However, this study established that EoE was associated with IgG4 and was not an IgE-induced allergy, by documenting granular deposits of IgG4, abundant plasma cells containing IgG4 and serum IgG4 levels reactive to specific foods among patients with EoE.

Recently, a case report has suggested some utility of vedolizumab, an anti-α4β7 integrin approved for IBD which blocks lymphocytes from binding to MAdCAM-1 on intestinal endothelial cells, to treat EoE, through its potential effects over the αEβ7 integrin / E-cadherin axis: A 43-year-old male who shared Crohn's disease and EoE experienced clinico-histologic remission of the latter after one year of therapy [91], thus opening the path to further research. In fact, recent experiences have also shown the effectiveness of vedolizumab in normalizing gastric or intestinal histology and symptoms derived in several cases of eosinophilic gastritis or gastroenteritis refractory to other drugs [92,93].

### *4.1. Blocking the IL-5 pathway to treat reduce eosinophilic infiltration*

IL-5 has a central, selective role in the proliferation, maturation and release of eosinophils from the bone marrow to the circulating blood [13], therefore it seemed one of the first therapeutic targets to be tested in EoE. Allergen-challenged mice by



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respiratory [94] or epicutaneous [95] routes developed experimental EoE characterized by overproduction of IL-5, blood eosinophilia and eosinophilic infiltration of esophageal tissues, which were proportional to serum concentrations of IL-5. When the *IL-5* gene was knocked out, the mice were protected from developing experimental EoE after allergen challenge [96]. In humans, the *IL-5* gene and its protein are upregulated in biopsied from patients with active EoE [58,84] and blood-circulating lymphocytes of these patients are able to produce significantly higher amounts of IL-5 that those obtained from healthy voluntaries following in vitro stimulation [97]. In addition, the proportion of blood-circulating IL-5+CD4 T cells in EoE patients correlates with the severity of esophageal tissue eosinophilia [98].

Anti-IL-5 treatments are effective as an adjunct to standard care in patients with severe eosinophilic asthma and poor control [99] and might provide some benefit to patients with nasal polyposis [100]. The IL-5 blocker mepolizumab was later tested in EoE patients through RCTs involving children [101] and adults [102], while reslizumab was evaluated in children only [103]: neither of them was superior to placebo in terms of symptom relief. Although a substantial decrease in esophageal eosinophilia was observed, peak eosinophil counts remained >20 eos/hpf and histological remission was not observed. More recently, the open-label extension of a pediatric trial with reslizumab showed that the eosinophil count improved along the treatment despite patients followed a relatively unrestricted diet [104], therefore suggesting a certain efficacy for this drug. However, a statistically significant reduction in symptoms versus the placebo group could not be demonstrated.

Benralizumab, an antibody that blocks the IL-5Rα receptor, has been approved to treat eosinophilic asthma in adolescents and adults after demonstrating a superior effectiveness compared to IL-5 blockers [99]. Despite it not yet being evaluated in EoE, an ongoing placebo-controlled RCT (NCT03473977) is investigating its efficacy and safety in eosinophilic gastritis and gastroenteritis.

### *4.2. The IL-13 pathway in the pathophysiology and treatment of EoE*

IL-13, a Th2 cytokine, plays a central role in several eosinophilic inflammatory disorders, including EoE. The expression of the *IL-13* gene is upregulated in blood eosinophils of atopic subjects [105], and especially in the esophageal epithelium of EoE patients. After being stimulated with IL-13, esophageal cells express and secret the eosinophil-activating chemoattractants eotaxin-1/CCL11 and eotaxin-3/CCL26, responsible for eosinophil recruitment and accumulation in the esophageal epithelium [106].



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IL-13 also promotes epithelial dysfunction in EoE by decreasing gene expression of desmosome proteins, basement membrane components and adhesion molecules [13]. The disruptive effects of IL-13 on the esophageal epithelium are regulated through the *CAPN14* gene, which is encoded in the EoE susceptibility locus 2p23. The *CAPN14* gene is dynamically upregulated by both IL-4 and IL-13 and exerts a gatekeeper role in EoE [107].

Two monoclonal antibodies targeting IL-13 (QAX576 and RPC4046) have been evaluated in EoE through phase II RCTs. The first study investigated QAX576 as a potential treatment of adult EoE and was published in 2015 [108]. Adult patients were randomly assigned to QAX576 (6 mg/kg) or placebo every 28 days for 3 IV intravenous infusions with 6-month follow-up. QAX576 led to a 60% decrease in mean intraepithelial eosinophil counts but reached no histologic remission; a nonsignificant trend toward improvement in dysphagia severity, as measured by the Mayo Dysphagia Questionnaire, was documented. In addition, QAX576 normalized the expression levels of some EoE-related genes, with changes differing between responders and nonresponders to the drug. The development of QAX576 has since been discontinued.

RPC4046 was assessed as a second monoclonal antibody to block IL-13 from binding to subunits alpha 1 (IL13RA1) and 2 (IL13RA2) of the IL-13 receptor. In a recently published placebo controlled RCT [45], 99 adult patients with EoE were assigned to either RPC4046 10 mg/kg IV loading dose followed by 360 mg SC once a week, 5 mg/kg IV loading dose + 180 mg SC once a week, or placebo in a 1:1:1 ratio for 16 weeks of therapy, with an optional open-label phase with the higher dose. After the double-blind period of 16 weeks, a statistically significant reduction in mean eosinophil count was observed in both RPC4046 groups compared with placebo. Peak esophageal eosinophil counts were significantly reduced, with 50% of patients treated with 180 mg and 360 mg having <15 peak eos/hpf compared with 0% placebo ($p<0.0001$ for both comparisons), and 25% of patients in the 180 mg RPC4046 group and 20% in the 360 mg RPC4046 group having <6 peak eos/hpf after treatment. Regarding symptom improvement, a non-significant trend in favor of RPC4046 was reported, particularly in dysphagia. Results from the open-label extension study showed a sustained symptomatic and histologic improvement at week 52 following successful induction therapy among patients treated with the 360 mg dose [109]. Long term assessment of the effectiveness of RP4046 in the sustained control of EoE is required.

### *4.3. Interleukin-4 receptor antagonists: An improved mechanism*



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In contrast to the expression of *IL-13 gene*, *IL-4* is not upregulated in the esophageal epithelium of patients with EoE compared to healthy controls [105]. However, both Th2 cytokines are closely related as their molecular structures are similar, and they share a 30% of their sequences. In fact, IL-4 and IL-13 have overlapping downstream effects [110] because both cytokines bind to a common heterodimeric receptor (IL-4Ra and IL-13Ra1). In this sense, therapies directed to IL-4 and IL-13 separately could be ineffective. Dupilumab is a monoclonal antibody directed against IL-4Ra, which represents the most promising IL-4/IL-13-targeted therapy to date. It is effective and has been approved to treat asthma [111] and atopic dermatitis [112], and ongoing trials are now evaluating dupilumab in EoE. A phase II, double-blind, placebo-controlled RCT (NCT02379052) was carried out with 47 adult patients with moderate-to-severe EoE to assess whether dupilumab was able to relieve symptoms after a 12- week treatment period [113]. Patients received either dupilumab 300 mg SC weekly following a 600-mg loading dose or placebo. At week 10, a significant improvement in the ability to swallow was reported by patients who received dupilumab reported compared to placebo (45% vs. 19% improvement from baseline in the Straumann's Dysphagia Symptoms Score; $p<0.05$). Esophageal eosinophil counts were significantly reduced by 107% from baseline in patients who received dupilumab compared with an increase of 14% in those who received placebo. Overall, 82.6% of patients reduce peak eosinophil counts below 15 eos/hpf and 65.2% had less than 6 eos/hpf. Patients treated with dupilumab significantly improved the endoscopic and histological activity scores of EoE. The compliance of the esophagus, measured by endoFLIP, increased accordingly. A currently ongoing phase III trial (NCT03633617) is assessing long-term efficacy and tolerability of dupilumab 300 mg doses every week or every two weeks compared to placebo in adults and adolescents with EoE. The studies of monoclonal antibodies in EoE reviewed above are summarized in **TABLE 2**.

### 5. Antiallergic drugs: Little to expect in EoE

Despite EoE being recognized as an allergic disease that shares many common physiological and clinical aspects with other Th2-type atopic diseases, the effect of antiallergic drug treatments on EoE have been disappointing. Thus, cromolyn, a mast cell stabilizer with poor absorption and almost nonexistent side effects, prevents the release of inflammatory mediators such as histamine from mast cells. In systemic mastocytosis, cromolyn is of choice to treat associated gastrointestinal symptoms, and in asthma, cromolyn significantly decrease activated eosinophils in bronchial mucosa, similarly to fluticasone propionate and better than placebo or beta-2 agonists [114,115]. However, no benefit from cromolyn on symptoms or inflammation was described for



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children with EoE in early case reports [116]. Recently, a RCT that assessed viscous oral cromolyn for EoE in 16 children showed no changes in esophageal or blood eosinophilia after an 8-week treatment, and no significant benefit over symptoms compared to placebo were noted [117].

Montelukast is used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies due it blocks the leukotriene D4 receptor. As Montelukast also inhibits mast cell degranulation in the skin [118] and gastrointestinal tract mucosa [119], it was therefore evaluated as a potential treatment for EoE. An open-label trial in children treated with montelukast given at standard doses no patient achieved histologic response, despite some symptomatic improvement was reported [120]. In adults, Montelukast was also not superior to placebo to maintain EoE remission [121,122].

Finally, prostaglandin D2 (PGD2) produced and released by mast cells, exerts downstream inflammatory effects via the CRTH2 receptor, promoting recruitment of inflammatory cells, including eosinophils [123]. OC000459 is a selective CRTH2 antagonist effective against eosinophilic asthma, which was evaluated in a double-blind placebo-controlled RCT in adult patients with EoE [124]: A significant decrease in both esophageal eosinophilia and symptoms was observed among the patients treated with the active drug, as well as a trend towards normalization of the endoscopic aspect of the esophagus. However, the esophageal mucosa did not return to normal.

## 6. Potential Therapeutic Targets for EoE

Unveiling the molecular mechanisms leading to EoE is allowing new therapeutic targets to be set against which new research efforts can be directed. Therefore, several molecules acting at different points could be of potential benefit for these patients.

Thymic stromal lymphopoietin (TSLP) is a cytokine mainly produced by epithelial components with a central role in several immune-mediated disease, which include inflammatory bowel disease, bronchial asthma, atopic dermatitis, and EoE [13]. TSLP is essential to activate antigen presenting cells, including food antigen-presenting dendritic cells in the esophageal mucosa. This will then induce Th2 polarization of naïve CD4 + T cells [125] towards the development of antigen-specific immune responses. Interrupting this pathway therefore appears as a relevant therapeutic target, and different antibodies have been evaluated in murine models of atopic diseases, especially in asthma and EE. Blocking CD4 Th2 development by anti-TSLP antibodies or antibodies that inhibit its receptor TSLPR may prevent esophageal eosinophilia and



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food-related symptoms in experimental EoE [126]. As for clinical research, tezepelumab or AMG 157 is a fully human anti-TSLP antibody with favorable effects in adult patients with uncontrolled asthma, according to a phase IIb RCT [127]. Because TSLP is also a potent chemoattractant for eosinophils, this product could also represent a promising pharmacological target for EoE.

Eotaxins are the most studied eosinophil chemoattractants and commonly bind to the CCR3 receptors. An oral small-molecule selective competitive antagonist of CCR3 (GW766994) has been investigated in airway eosinophilia, with negative results [128]. As yet, no studies in EoE with these drugs have been proposed.

Sialic acid-binding immunoglobulin-type lectins, or Siglecs, can be found on the membrane of eosinophils and other types of immune cells. An important role in eosinophil apoptosis and clearance has been recognized for Siglec-8, which also inhibits mediators release from mast cells and reverse tissue remodeling. The administration of anti-Siglec-8 monoclonal antibody to a murine model of eosinophilic gastroenteritis significantly reduced eosinophils and mast cells in the stomach, small intestine, and mesenteric lymph nodes and decreased levels of inflammatory mediators [129]. After this promising results, ongoing trials of two anti-Siglec-8 antibodies, AK001 and AK002, are being currently assessed in nasal polyposis, systemic mastocytosis, and keratoconjunctivitis (NCT02734849, NCT02808793, NCT03379311). An additional phase II, placebo-controlled RCT of AK002 is currently recruiting adult patients with eosinophilic gastritis and/or gastroenteritis (NCT03496571).

Finally, losartan, an angiotensin II receptor blocker used to treat high blood pressure in children and adults, has demonstrated an ability to reduce the signaling of TGF-β thus constituting a potential treatment for fibrosis in EoE [13]. A Phase II trial with increasing doses of losartan is currently been tested to evaluate endoscopic, histological and symptomatic improvement in EoE (NCT03029091).

## 7. Expert Opinion

The treatment of EoE has possibly generated the most change in recent years [1]. Currently, dietary treatment, PPIs and swallowed topical corticosteroids represent first-line effective therapies for EoE, with no direct comparative study allowing prioritization of one over the others. This determines the need to customize the choice of treatment according to patients' characteristics and provider's resources. Controlling inflammation reduces the need for repeated endoscopic dilations [130]. Properly managed, the currently available therapeutic options have allowed symptoms and eosinophilic inflammation of a high proportion of patients to be resolved in a sustained manner, and



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after the release of novel formulas of topic steroids targeted to the esophageal mucosa, only a minority of patients will be considered as refractory.

However, regardless of having been able to achieve an acceptable degree of disease control, the limitations of the current EoE treatment options are now being revealed. Dietary treatment is the only drug-free one that directly targets the primary cause of EoE, able to achieve and maintain disease remission [16]. Rather than fostering progress to rationalize its use and improve its acceptance by patients [78], or trying to develop novel modalities for determining food triggers, the focus has centered on the areas of controversy it still generates, including issues of cross-contamination and "dosing" of how much food to avoid or add back, costs and potential effects on quality of life, long-term efficacy, and the risk of developing immediate IgE-type reactions after initial dietary elimination [131].

Recognizing the role of PPIs in the treatment of EoE [57], and their ability to rid a moderate proportion of patients of inflammation and symptoms through a cheap and, in general, safe drug has been more complex. It is often noted as a limitation that PPIs are not specifically approved for this indication [132] or that their role in the long-term EoE treatment algorithm is unclear [81] (as if this was not a common characteristic of any other drug), in order to relegate its use in favor of more expensive options. As for topic corticosteroids, the use of novel formulations designed to coat the esophageal mucosa has been shown to reduce the dose required to achieve and maintain EoE remission in the long term [21,71], but withdrawal is likely to induce a rapid recurrence of the inflammation, so they should be considered as long-term therapies. Contrary to systemic steroids, budesonide and fluticasone are considered safe when used in the long term, even for children, with no significant risk of adrenal suppression or bone fracture, as demonstrated in patients with asthma and ulcerative colitis [133-135]. However, the need for steroid-sparing therapies in EoE remains. Novel biologics could therefore overcome some of the limitations of current therapies as well as dispense with diets and the taking of daily medicines.

Despite the enormous therapeutic potential of biologics, the risk of immune-mediated effects by virtue of their action mechanism is potentially significant: hypersensitivity reactions, overstimulation, immune imbalance-derived reactions and cross-reactivity have been described [136]. Immunogenicity, leading to loss of response due to neutralizing antibodies, requires increased doses, shortened administration intervals or associate immunosuppressants, and is a common problem for several biologics [137]. Biologic drugs targeting Th2-mediated inflammation have fewer reported side effects,



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though many are new and emerging drugs whose adverse effects may materialize with more use. Therefore, continued long-term safety monitoring is required [138]. As with all therapies, the risks associated with side effects of biologics must be balanced against the benefits these drugs offer for EoE. Certainly, currently available biologics that target the Th2-mediated immune response have a much better safety profile than long-term therapy with systemic steroids, but the latter are not recommended in EoE [1]. In any case, novel biologic therapies under investigation for EoE should be considered as convenient alternatives for patients also suffering from bronchial asthma, persistent rhinitis or difficult-to-control dermatitis, who may benefit from a single treatment able to simultaneously control several diseases.

Cost has not yet been adequately addressed: initial studies have shown it would triple that of controls in the same age group. These are mainly in relation to frequent doctor visits, diagnostic delays, requirement for upper endoscopy with biopsy for diagnosis and monitoring of disease activity, and medications currently used off-label [139]. More expensive therapies could further trigger costs for insurance companies and health systems, as cost-effective studies for the different therapies have not been published to date.

In addition, combinations of different treatments for patients partially responding to single treatments are still to be explored, as well as intermittent versus continuous maintenance therapy. Alternate therapeutic options at different stages of the disease, as with other chronic diseases, also needs to be considered.

Several drugs to treat EoE will be approved by regulatory agencies in the coming years, joining the new budesonide orodispersible tablet already approved by the European Medicines Agency. The possibility of incorporating all into the real-world practice will largely depend on the costs for the healthcare systems and patient profiles. In the meantime, we will be able to measure the impact of EoE and its therapy, in order to develop cost-effectiveness studies for long-term treatments. The design of rational and realistic strategies for initial and maintenance treatments of EoE should start from a patient-centered approach and shared decision-making model, while also trying to achieve appropriate long-term monitoring, reduction in the burden of disease for all patients and health systems, and prevention of complications from EoE.

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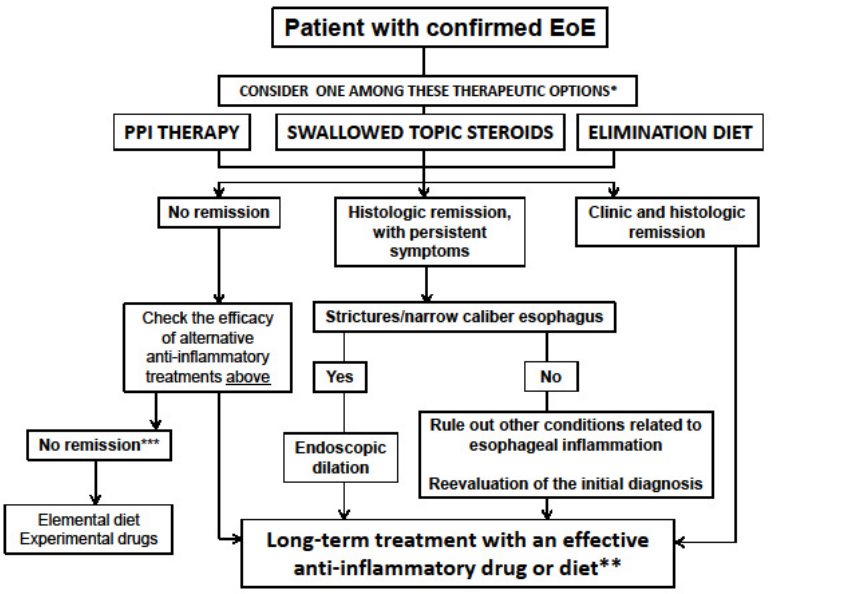
## Figure legend

**Figure 1.** Evidence based-therapeutic algorithm for treating eosinophilic esophagitis in clinical practice




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

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**TABLE 1.** Swallowed topical steroid initial dosing for eosinophilic esophagitis treatment. Adapted from [1].

| Drug | Target population | Induction dosing (usually divided doses) | Maintenance dosing (usually divided doses) |
|---|---|---|---|
| Fluticasone propionate [a,b] | Children [d]<br><br>Adults | 880-1760 mcg/day<br><br>1760 mcg/day | 440-880 mcg/day<br><br>880–1760 mcg/day |
| Budesonide [b,c] | Children [d]<br><br>Adults | 1-2 mg/day<br><br>2-4 mg/day | 1 mg/day<br><br>2 mg/day |
| Budesonide orodispersible tablet [e] | Adults | 2 mg/day | 1 mg/day |

[a] If an inhaler is used, the patient should be instructed to puff the medication into their mouth during a breath hold.

[b] Regardless of the form of administration (nebulized or swallowed), patients should fast at least 30–60 min after medication in order to minimize esophageal drug clearance.

[c] Oral viscous budesonide preparation consists of mixing 1–2 mg budesonide with 5 mg of sucralose or similar.

[d] Specific doses in children will be determined by age, height or weight.

[e] Available in several European countries

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**TABLE 2.** Clinical studies evaluating monoclonal antibodies for the treatment of eosinophilic esophagitis

| Study | Reference | Target | Monoclonal antibody | Mechanism of action | Design | Population (sample size) | Dosage | Histologic response | Clinical response | Tolerability |
|---|---|---|---|---|---|---|---|---|---|---|
| Straumann et al, 2011 | [69] | TNF-α | Infliximab | Binds TNF-α | Open label case series | Adults (3) | Two infusion of 5 mg/kg every other week | No changes in peak eosinophil counts | Symptoms improved in 2 patients but impaired in the remaining one | Well tolerated |
| Straumann et al, 2010 | [102] | IL-5 | Mepolizumab | Binds IL-5 | Placebo-controlled, phase 2 RCT | Adults (11) | Two infusions of 750 mg active drug or placebo weekly. Two more infusions of 1500 mg active drug or placebo in case of no histologic response | No patient achieved histologic remission. 54% redution on mean eosinophil count in mepolizumab group. 5% reduction in mean eosinophil count in placebo group | No significant differences in symptoms improvement compared to placebo | Few mild AE no related with active drug |
| Assa'ad et al, 2011 | [101] | IL-5 | Mepolizumab | Binds IL-5 | Placebo-controlled, phase 2 RCT | Children (59) | Three infusion of 0.55, 2.5, or 10 mg/kg monthly, or placebo | 8.8% of patients achieved histologic remission (<5 eos/hpf) 89.5% of patients achieved <20 eos/hpf Better results with the highest dose | No significant improvement in symptoms | No related AE |
| Spergel et al, 2012 | [103] | IL-5 | Reslizumab | Binds IL-5 | Placebo-controlled, phase 2 RCT | Children (22) | Four infusions of 1, 2 or 3 mg/kg monthly, or placebo | Peak eosinophil counts reduced by 59%, 67 and 64%, in the 1, 2 and 3 mg/kg groups, respectively. Patients under placebo reduced peak eosinophil count by 24%. Most patients had >5 eos/hpf at end of treatment | Non-significant improvements in symptoms were observed in all treatment groups, which were not associated with changes in esophageal eosinophil counts. | Well tolerated, being headache and cough the most common AE |
| Markowitz et al 2018 | [104] | IL-5 | Reslizumab | Binds IL-5 | Open-label extension of RCT | Children (9) | 2 mg/kg monthly | 92% of patients had peak eosinophil count <5 eos/hpf at end of treatment | positive response to symptoms related to EoE at last infusion | No serious AE were attributed to reslizumab |
| Clayton et al, 2014 | [90] | IgE | Omalizumab | Binds free IgE | Placebo-controlled phase 2 RCT | Adults (3) | 0.016 mg/kg/IgE every 2–4 weeks, depending on body weight, for | 33% achieved peak eosinophil count <15 eos/hpf More effective in children than in adults | Some clinical improvement: 47% Clinical remission in 1/3 patients | No serious AE, high drop out because lack of |

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| | | | | | | | 12 weeks | | | efficacy |
| Rothenberg et al, 2015 | [108] | IL-13 | QAX576 | Binds IL-13 and inhibits eotaxin production | Placebo-controlled phase 2 RCT | Adults (25) | Three infusion of active drug 6 mg/kg monthly or placebo | Peak eosinophil count decreased by 60% in the active group but increased in the placebo group.<br>No benefit to achieved >75% reduction in esophageal eosinophil counts compared to placebo was observed. | QAX576 showed a non-significant trend to symptomatic improvement | Mild AE: cough and GERD symptoms |
| Hirano et al, 2019 | [45] | IL-13 | RPC4046 | Binds IL-13 | Placebo- controlled, phase 2 RCT | Adults (99) | 180, 360 mg or placebo weekly for 16 weeks | 50% of patients in both active arms had <15 eos/hpf after treatment (0% in the placebo arm).<br>25% of patients in the 180 mg RPC4046 group and 20% in the 360 mg RPC4046 had <6 eos/hpf after treatment | The group treated with 360 mg showed a non-significant reduction in symptoms | No serious AE |
| Dellon et al, 2019 | [109] | IL-13 | RPC4046 | Binds IL-13 | Open-label extension of a RCT | Adults (86) | 180 or 360 mg weekly for 52 weeks | Peak eosinophils in 180 and 360 mg arms remained stable regarding prior to OLE phase, but improved greatly among patients allocated to active drug 360 mg after placebo | sustained symptomatic improvement at week 52 among patients treated with the 360 mg dose | No safety concerns through 52 weeks |
| Hirano et al, 2017 | [113] | IL-4/IL-13 | Dupilumab | Binds the α-subunit of the IL-4 receptor (inhibits IL-13 receptor) | Placebo- controlled, phase 2 RCT | Adults (47) | 300 mg or placebo weekly for 12 weeks | Peak eosinophil count reduced by 91.8% in the dupilumab arm vs 15.1% increase in the placebo arm<br>78.3% of patients treated with dupilumab achieved <15 eos/hpf<br>60.9% of patients treated with dupilumab achieved <6 eos/hpf | No reported | No serious AE |
| Nhu et al, 2018 | [91] | MAd-CAM1 | Vedolizumab | Binds α4β7 integrin | Single case report | Adult (1) | 300 mg form induction at 0.2.6 weeks, and every 8 weeks, for 1 year | Peak eosinophil count reduced from 30 to 2 eos/hpf | Improvement of dysphagia | Well tolerated |

AE: Adverse events; RCT: randomized clinical trial

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