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Biological Therapies for Eosinophilic Gastrointestinal Diseases

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Abstract

The scientific basis and the clinical application of monoclonal antibody therapies that target specific immunologic pathways for eosinophilic gastrointestinal diseases (EGIDs) are areas of active interest. There is a growing recognition of a subset of patients with eosinophilic esophagitis, or EoE, whose disease does not respond well to topical steroids or elimination diets. In addition, long-term use of corticosteroids presents risks. Systemic therapy with a biologic agent offers potential advantages as a global approach that could limit the need for multiple, locally active medical therapies and allergen avoidance. The identification of novel biologic strategies is ongoing, and the recent validation of instruments and outcome measures to assess disease activity has proved essential in demonstrating efficacy. Studies using biologics that target IL-13 pathways in the treatment of EoE have demonstrated substantial promise.

Keywords

Eosinophilic esophagitis; gastroesophageal reflux disease; dysphagia; food allergy; esophageal stricture; esophagitis

Introduction

At present, our therapeutic options for eosinophilic esophagitis (EoE) include medications, elimination diets, and esophageal dilation. Medical therapeutics consist primarily of orally administered topical corticosteroids. Several randomized, controlled trials support the efficacy of topical corticosteroids, although the histologic response rates have varied, ranging from 40 to 90%[1–6]. To date, however, topical corticosteroids are not approved by the Food & Drug Administration (FDA) for the treatment of EoE. As a result, many clinicians

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are using preparations designed for asthma. A limited number of studies regarding long-term topical corticosteroid use have raised concerns regarding its effectiveness, particularly in the setting of attempts at dose reduction,[7–9] and long-term adverse effects such as adrenal insufficiency[10]. For EGIDs that affect the stomach, small intestine, and colon, systemic corticosteroids are widely utilized with well-known adverse effects associated with prolonged administration[11]. Biologic therapies introduce novel approaches that target specific immune pathways and potentially address several unmet needs in the management of EoE and EGIDs. This review summarizes the therapeutic potential, scientific rationale, and available clinical trial data regarding past, present, and future biologic treatments.

Therapeutic Endpoints in EoE Clinical Trials

The interpretation of clinical trials of novel therapeutics in EGIDs relies upon the application of appropriate and validated endpoints, and the lack of an accepted set of clinical outcome metrics (COMs) for defining successful response to therapy impedes progress. Currently, focus lies on the co-primary endpoint of symptom assessment using patient reported outcome (PROs) instruments and histologic assessment of peak mucosal eosinophil density (eosinophils per high power field). The tools used to assess symptoms and histopathology, however, have varied considerably and have been largely unvalidated. Over the past several years, several PRO instruments have been designed and validated for evaluation of symptoms and QOL in both pediatric and adult EoE. For adults, validated instruments include the Daily Symptom Questionnaire (DSQ) and EoE Activity Index (EEsAI)[12]. For children, the Pediatric EoE Symptom Score (PEESS) has been validated but it has not yet been evaluated in terms of patients' responsiveness to therapy[13]. Unfortunately, most of these validated tools were not available during the design of many clinical trials under current discussion.

While symptom assessment is a logical endpoint for trials in EoE, it is important to emphasize limitations to this measurement of outcome. Prolonged mastication, extended meal times, and avoidance of harder textured foods (e.g., meat, bread) can mitigate the intensity of dysphagia and lead to inaccurate assessment of disease activity. Another major concern lies in the relationship between symptoms and esophageal remodeling. Esophageal remodeling related to chronic inflammation manifests as esophageal strictures that are a major determinant of symptom outcomes of dysphagia and food impaction[14]. The ability of anti-inflammatory or immune therapies to reverse fibrostenosis is unproven in EoE, requiring such therapeutics to relieve dysphagia may overlook therapeutic benefits in preventing other disease consequences. The clinical observation that symptoms of dysphagia can be effectively ameliorated in over 90% of patients with esophageal dilation, without altering the underlying inflammatory response, supports this view[15].

Randomized controlled trials have demonstrated that measuring EoE activity using esophageal mucosal eosinophil density offers an objective and quantifiable measure with a high degree of inter-observer agreement and with minimal placebo response Outcomes are commonly defined by a reduction in mucosal eosinophilia, but the method used to calculate eosinophil density has varied considerably. Furthermore, a variety of target thresholds have been used including endpoints of <15, < 10, < 6, and <5 eosinophils per high power field

(eos/hpf) in some studies and percent reduction in eosinophil density in others. The recent development and validation of an EoE Histologic Severity Score (EoE-HSS) that incorporates histopathology beyond eosinophil density including basal cell hyperplasia, dilation of intercellular spaces and subepithelial fibrosis provides a more comprehensive and accurate characterization of mucosal inflammation in EoE for clinical trials[16]. While it is tempting to consider use of histology as the primary determinant of therapeutic efficacy, a marked dissociation between symptoms and pathology is well-recognized. This dissociation is likely explained by modification of eating behavior, subepithelial remodeling that is poorly assessed with standard biopsy technique, and a symptom-placebo response.

Endoscopic outcomes serve as primary determinants of therapeutic efficacy in GERD and inflammatory bowel disease, and increasing data supports their use as an objective endpoint in clinical trials of EoE. The EoE Endoscopic REFerence Scoring system, or EREFS, is a classification and grading system that has been validated and shows a high degree of accuracy in the diagnosis of EoE in children and adults[13, 17, 18]. Recent clinical trials of topical steroids optimized for esophageal delivery as well as phase 2 trials of biologic therapies have demonstrated responsiveness of EREFS in assessment of mucosal healing[19–21].

Other investigations are actively evaluating biomarkers of EoE disease activity beyond mucosal healing and symptoms. mRNA expression provides a molecular fingerprint of key upregulated and downregulated genes in esophageal biopsies of EoE that is distinct from the signature identified in control subjects and patients with GERD[22]. The Eosinophil Diagnostic Panel (EDP) includes clusters of genes that depict T_H2 inflammatory response, mast cell activation, and fibrosis pathways. Reversal of the EoE pattern has been demonstrated in the setting of randomized controlled trials using topical fluticasone in children and anti-IL-13 therapy in adults. The EDP offers potential for examining molecular pathways that may provide insights into EoE pathogenesis, inform a personalized approach to therapy, and improve diagnostic accuracy. For whole organ assessment of esophageal remodeling, the functional lumen imaging probe (FLIP) is a catheter-based technology performed during an endoscopic examination that applies impedance planimetry to measure of esophageal biomechanical properties in EoE[23]. Initial studies demonstrated reduction in esophageal mural distensibility that was associated with an increased risk of food impaction[24, 25]. Preliminary studies using FLIP have demonstrated a significant improvement in esophageal distensibility following administration of topical corticosteroids and anti-IL-4 receptor antibody therapy[21, 26].

Targets without published trials

Siglec-8—While published clinical trials do not exist for Sialic acid-binding Ig-like lectin 8 (Siglec-8), its exclusive expression by eosinophils and mast cells makes it an interesting therapeutic target for EGIDs. Blockade of Siglec-F, the murine homolog in experimental murine eosinophilic disease, led to a reduction of eosinophils in the esophagus. This was associated with decreased angiogenesis, deposition of fibronectin, and basal zone hyperplasia, which are key aspects of EoE pathogenesis[27]. More importantly, engagement of Siglec-8 induces eosinophil cell death and decreases mediator release by mast cells[28].

Recent abstracts presented at the 2018 AAAAI meeting demonstrated that in a mouse model of eosinophilic gastritis, a novel antibody that targets Siglec-8 (AK002) resulted in selective depletion of tissue and blood eosinophils and a reduction in mast cells.[29, 30]. A clinical trial is further investigating the direct role of Siglec-8 in EGIDs.

TSLP—Two genomics studies initially identified TSLP single nucleotide polymorphisms in patients with EoE[31, 32]. More recent studies have confirmed this risk factor TSLP expression is increased in EoE patients as compared to controls in the differentiated supra-basal layer of the epithelium. Noti et al. examined TSLP function in murine experimental EoE associated with food impaction, and their data suggest that TSLP recruits basophils with downstream effects on IL-4 and ultimately eosinophils[33]. TSLP enhances the migration of eosinophils, likely in combination with IL-33, which enhances IL-5 and IL-13 production[34]. Importantly, blockade of TSLP pathways abated the eosinophilic inflammation and food impaction in the murine model. Gauvreau et al. reported on a double-blind placebo-controlled study of Tezepelumab (AMG 157), a human monoclonal IgG2 antibody against TSLP, for use in the treatment of allergic asthma[35]. The authors observed a reduction in early and late asthmatic responses, although the potential utility for EGIDs is unclear due to limited data regarding the role of TSLP.

Integrins—While they have not been well-studied in EGIDs, integrins have offered a therapeutic target in inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis. Erie et al described the alpha4beta7 integrin on leukocytes in 1994.[36] This integrin plays a role in eosinophil recruitment to the intestine[36, 37] and in intestinal mast cell hyperplasia[38, 39]. Forbes et al. reported that the beta2 integrin factors in colonic eosinophil recruitment[40], suggesting that a role in lower EGIDs may also be a consideration. Cadherin 26 was recently found to be increased in pathologic allergic inflammation including that of EoE, and data suggested it enhances cellular adhesion to alpha4beta7 integrin and binds directly to alphaE and alpha4[41]. This modulated CD4 T-cell activation, which is critical in EGIDs, underscores potential for integrin targeting. A recent retrospective series described improved histopathology in 5 patients with EGID following therapy with vedolizumab, but exposure to corticosteroids may have affected the responses[42]. The results of further studies are nonetheless awaited.

Eotaxins—Eotaxins, produced in large part by epithelial cells, play a crucial role in the chemotaxis of eosinophils to tissue. Activated eosinophils, mast cells, and fibroblasts are also capable of producing eotaxins[43], although the relative contribution of each cell type is unclear. Eotaxins can be modulated by mast cell proteases[44], and their production depends on STAT6 in response to IL-4 and IL-13[45]. Of the eotaxins (1–3), CCL26/eotaxin-3 is among those that are most highly expressed in the EoE transcriptome[46], and glucocorticoids downregulate it.[47, 48]. Mice that are deficient in the eotaxin receptor have been observed to be protected from experimental EoE[46]. Interestingly, omeprazole blocks STAT6 binding to the promotor of eotaxin-3 in epithelial cells[49, 50].

TGF-β1—TGF-β1 has long been known to hold a critical profibrotic role in the pathogenesis of EoE. Muir et al. examined fibroblasts that were treated with TGF-β1 and

observed increased markers of fibrosis[51]. Notably, the stiffness of the matrix affected response to TGF-β1, suggesting that increased rigidity with disease chronicity may exacerbate fibrosis development. Aceves et al. identified TGF-$\beta1^+$ mast cells in the smooth muscle layer[52]. Notably here, TGF-β1 enhanced smooth muscle contraction, likely via phospholamban[53], which supported a contribution to disease symptoms. Blockade of TGF-β1 signaling in human esophageal fibroblasts and muscle cells led to reduced fibronectin and collagen.[54] TGF-β1 is also active in the epithelial layer of the esophagus. Nguyen et al. recently reported that TGF-β1 alters epithelial barrier function via claudin-7[55], and Rawson et al. found a role in PAI-1 signaling[56]. Together, the data suggest that TGF-β1 may prove a useful target in patients with persistent symptoms that are associated with fibrotic disease. A multicenter, proof-of-concept study is currently investigating the effectiveness of losartan, an anti-hypertensive agent that has been demonstrated to inhibit the effects of TGF-β in experimental models[57].

Targets with published trials

IgE—Classic T_H2 pathology such as that underlying allergic asthma involves production of antigen-specific IgE, which binds to mast cells and basophils and degranulates upon cross-linking from antigen binding[58]. IgE holds a clearly defined role in immediate hypersensitivity reactions that yield acute or sub-acute respiratory, dermatologic, and intestinal symptoms and can be life-threatening, but its function in EoE or EGIDs is less clear. Numerous studies have examined the presence of food-specific IgE, which is not universal among those with EoE and often does not correlate with food triggers[59]. For many patients, elevated IgE represents allergic sensitization that is associated with immediate hypersensitivity responses[60, 61]. Pelz et al. found that food-specific IgE levels were increased in EoE patients with a clinical history that was consistent with immediate hypersensitivity as compared to EoE patients without such symptoms[60]. Notably, EoE dietary triggers were low as compared to triggers of immediate hypersensitivity, suggesting that systemic IgE responses are not a driving factor of eosinophilia. Not surprisingly, several groups have found no change in phenotype of murine experimental EoE when either B-cells or the IgE heavy chain was deficient[33, 62]. Vicario et al. did find evidence of esophageal plasma cells that produce IgE, and local IgE effects may contribute to EoE pathogenesis[63]. Patients with EoE are also commonly sensitized to aero-allergens. This may trigger esophageal inflammation directly and drive food sensitivity through cross-sensitization[64, 65].

There is limited data to support the clinical use of anti-IgE therapy for EGIDs. A single-center, randomized, double-blind, placebo-controlled trial in which an anti-IgE antibody (omalizumab) was delivered for 16 weeks failed to demonstrate improvement in either symptoms or esophageal eosinophilia in 30 adults with EoE[66]. The authors took previous data demonstrating the poor sensitivity and specificity of IgE-based testing in predicting specific food triggers to EoE into account and concluded that EoE is not primarily an IgE-induced allergic response. A smaller proof-of-concept study examined the effectiveness of omalizumab treatment of 9 subjects with EGID[67]. While eosinophil counts decreased in both the stomach and duodenum (69% and 59% respectively), the differences were not significant. Symptoms, basophil expression and free serum IgE levels significantly

improved, however, raising the possibility that such treatment may be more effective for patients with EGID than for those with EoE.

CRTH2—Chemoattractant receptor-homologous molecule on T_H2 cells (CRTH2) is a receptor for prostaglandin D2 (PGD2)., PGD2 is produced by mast cells, and elevated levels have been observed in the plasma of EoE patients as compared to control subjects.[68] A variety of inflammatory cells including eosinophils, basophils, type 2 innate lymphoid (ILC2) and T-helper type 2 (Th2) cells express CRTH2[69]. It has a well-described role in cell chemotaxis and activation[28], and it has been appreciated to promote inflammatory severity in atopic animal models[70, 71].

A RDBPCT was conducted in 26 adults with EoE using OC000459, a selective, orally administered CRTH2 antagonist[72]. At the conclusion of an 8-week treatment period, the study achieved its primary endpoint of reduced esophageal eosinophil counts. OC000459 treatment significantly reduced mean eosinophil density (114.83 to 73.26 eos/hpf; p=0.0256), an effect that did not similarly transpire with placebo. The histologic improvement, however, was modest compared to other clinical trials in EoE. Furthermore, the degree of symptom improvement was similar between active drug and placebo, and endoscopic features did not improve.

IL-5—The cytokine IL-5 has a recognized central role in chronic T_H2 inflammation that occurs in EGIDs. Desreumaux et al. initially appreciated such a T_H2 response in lower EGIDs such as EGE in 1996[73], and Straumann et al later described its role in EoE.[74] Studies since have confirmed these findings[75–79]. IL-5 is predominant in the GI tract amongst patients with EGIDs as compared to those with immediate hypersensitivity[80]. It is a well-characterized element of the EoE tissue cytokine profile that is reduced with treatment such as corticosteroids.[47, 48] Studies utilizing transgenic over-expression and deficiency of IL-5 in mice have identified effects on eosinophil progenitor maturation, priming for chemokine stimulation to eotaxins CCL11, CCL24, and CCL26, and tracking to tissue[81–84]. IL-5 may also have role in remodeling when it is chronically overexpressed, as CD2-IL5 mice have increased collagen accumulation in the lamina propria and extended stromal papillae.[82] Sources of IL-5 include T_H2 cells, innate lymphoid cells (ILC2), mast cells, and eosinophils. ILC2 cells have been suggested to interact with mast cells[85], and T-cells express IL-5 along with the activation marker CD154 in response to EoE food triggers such as milk[75]. IL-5 thus functions to increase eosinophil cell density in the tissue, making it an important potential target in the treatment of EGIDs.

Biologic therapies targeting interleukin-5 (IL-5) have demonstrated efficacy in hypereosinophilic syndromes and eosinophilic asthma. The use of mepolizumab, a humanized, anti-IL-5 monoclonal immunoglobulin G1 antibody, in EoE treatment was first reported in an open label, phase 1–2 study of 4 adults[86]. The study demonstrated significant reductions in peripheral and esophageal eosinophilia and improvement in clinical outcomes. A randomized, placebo-controlled, double blind trial of mepolizumab in 11 adults with EoE for 8 to 16 weeks followed.[87] The authors reported histologic efficacy, with a 54% reduction in mean esophageal eosinophil counts, but no patient achieved the primary endpoint of

reduction of peak eosinophil counts to less than 5 eos/hpf. Moreover, no patient achieved the threshold of < 15 eos/hpf, and findings did not demonstrate symptom improvement.

An international, multicenter, double-blind randomized trial investigated the effect ofmepolizumab therapy in pediatric EoE.[88] Patients received one of three different dosing arms of mepolizumab every 4 weeks, for a total of three infusions with assessment. While a placebo arm was not used, the lowest dose was chosen to be minimally effective and to serve as a comparator. The primary endpoint was the proportion of patients with peak eosinophil counts of < 5 eos/hpf at week 12. The symptom endpoint was based on a non-validated daily PRO. While peak eosinophil counts did significantly decrease from 122.5 to 40.2 eos/hpf, the primary endpoint was achieved in only 8.8% of patients. Furthermore, significant improvement in symptoms was not detected across dosing arms.

In one of the largest randomized, placebo-controlled trials of EoE treatment, 226 children with the condition received reslizumab, a humanized monoclonal antibody to IL-5.[89] The study compared three different dosing arms that were delivered every 4 weeks to placebo. The co-primary endpoint consisted of a reduction in eosinophil counts and physician global assessment at week 15. Significant reductions in peak eosinophil counts were demonstrated, ranging from 59% to 67% compared with 24% for placebo. However, fewer than 25% of subjects achieved the threshold of < 15 eos/hpf and no change was observed in physician global assessment of those who had received the drug as compared to placebo.

The current literature indicates that therapeutic agents targeting IL-5 have demonstrated statistically significant although relatively modest reductions in esophageal eosinophilic inflammation. These agents have been well tolerated in all four short-term induction studies. The inability to demonstrate improvement in symptom outcomes may reflect the heterogeneous symptoms in pediatric EoE, lack of validated PRO instruments in pediatric EoE, issues with a higher than anticipated placebo response rate, limited reversibility of fibrotic remodeling, and involvement of cell types other than eosinophils in disease pathogenesis. The limitations of mepolizumab and reslizumab to achieve < 15 eosinophils per high-powered field in the majority of patients may be due to insufficient ability to deplete existing tissue eosinophils; additionally, longer duration of therapy may be needed. Benralizumab, which binds to IL-5 Receptor alpha on eosinophils, is afucosylated and results in more marked depletion of eosinophils by enhanced antibody-dependent cell-mediated toxicity.[90] It was recently approved for add-on maintenance therapy for severe eosinophilic asthma. Preliminary data demonstrated clinical and histologic efficacy in a small series of patients with EGID and hypereosinophilic syndrome[91]. We await future studies regarding the clinical efficacy of benralizumab in the treatment of EGIDs.

IL-13—IL-13 has many functions as an activator of the esophageal T_H2 inflammatory response, and it is produced by both T_H2 cells and activated eosinophils[74, 76, 92]. The IL-13 signature of the EoE transcriptome is largely replicated in IL-13-treated epithelial cells, and it reverses with corticosteroid therapy.[93] IL-13-mediated epithelial stimulation induces eotaxin-1, eotaxin-2, and eotaxin-3 expression via STAT6, thus contributing to eosinophil recruitment[94]. This essential role of IL-13 in eosinophil recruitment, via eotaxin production, has been confirmed in experimental murine EoE models using IL-13 deficient mice.

Additionally, intra-tracheal IL-13 can induce esophageal eosinophilia in mice[95], and stimulation of fibroblasts facilitates eosinophil recruitment via periostin, which enhances adhesion to fibronectin[96]. Beyond cell recruitment, IL-13 has a role in barrier function. It reduces epithelial differentiation including down regulation of desmosomal cadherin desmoglein-1 (DSG1),[97] and increases expression of the intracellular calcium-dependent protease calpain-14 (CAPN14)[98], leucine-rich repeat-containing protein 31 (LRRC31)[99], and the cytoskeletal protein synaptopodin (SYNPO)[100]. A role in esophageal remodeling has also been described via enhancement of collagen deposition[101], along with epithelial autophagy in a ROS-dependent manner[102], and induction of IgE expression[103]. Thus IL-13 has a pleotropic role in eosinophil recruitment, barrier dysfunction, and esophageal remodeling, and it may offer an appreciable target for biologic therapy.

Three clinical trials have evaluated the efficacy of anti-IL-13 antibody therapy. Two trials utilized monoclonal antibodies targeting IL-13 while the third targeted both IL-13 and IL-4 signaling. QAX576, a monoclonal IgG1 antibody to IL-13, was reported in a randomized double blind, placebo-controlled trial of 23 adults with EoE[104]. The proportion of patients who achieved the study's primary endpoint of a greater than 75% reduction in peak esophageal eosinophil counts at week 12 with QAX576 treatment was not significantly different from those who had received placebo. It should be noted that the study did not use validated endpoints, as it was one of the earliest trials of a biologic agent in treating EoE. In support of a key role for IL-13, the mean eosinophil counts significantly decreased by 60% with QAX576 treatment as compared with a 23% decrease with placebo, and expression of a series of relevant esophageal gene transcripts improved.

More recently, a randomized, double-blind, placebo controlled, 16-week trial in 99 adults with EoE reported the efficacy of RPC4046, a humanized monoclonal IgG1kappa anti-IL-13 antibody.[105] The primary endpoint of reduction of mean esophageal eosinophil counts was over 90 eos/hpf with active drug as compared to 4 eos/hpf with placebo ($p \leq 0{\cdot}0001$). The study noted significant improvement in endoscopically identified esophageal features of EoE and a trend for improvement in symptoms of dysphagia using validated instruments (EREFS, EEsAI). Of note, greater symptom improvement was found in patients whose disease was identified as steroid-refractory.

IL-4 receptor—IL-4 is a well-described T_H2 cytokine that has been observed at increased levels in EoE patients.[106] It is an allergic disease genetic risk locus[107], although its exact role in EGIDs is not yet clear. In allergic disorders, IL-4 coaxes naïve T-cells to become T_H2 cells and facilitate B-cell class switching to IgE. A variety of cells produce it, including T_H2 cells, activated mast cells, and eosinophils. IL-4 stimulation of the epithelium leads to production of eotaxin-3 via STAT6, thus contributing to eosinophil recruitment. The mechanism is similar to that of IL-13 and it is blocked by omeprazole[94]. This may explain the anti-inflammatory effect of PPIs in some patients. As IL-4 shares a common heterodimeric receptor with IL-13, therapy that targets IL-4 signaling through IL4Ralpha will affect both IL-4 and IL-13 pathways and may prove efficacious.

Dupilumab, a fully human, anti-IL-4 receptor alpha monoclonal antibody that inhibits signaling of IL-4 and IL-13, was recently approved for the treatment of adults with moderate

to severe atopic dermatitis. The results of a phase 2, multicenter, double-blind, randomized, placebo-controlled trial in adults with EoE were recently reported[21]. The study met the primary endpoint of significant improvement in symptoms of dysphagia as well as secondary endpoints regarding esophageal eosinophil counts, endoscopic features (EREFS), and comprehensive histologic scoring (EoE-HSS). The authors reported that 82.6% of patients achieved the threshold of < 15 eos/hpf at week 12 with dupilumab as compared to none with placebo.

Collectively, the recent trials of biologics directed at IL-13 and IL-4 have demonstrated significant reductions in esophageal eosinophilia and improvement in symptoms of dysphagia. Although direct comparisons are not possible due to differences in methodology, the reported histologic improvements appear more substantial than those that have been reported in previous trials of biologic agents with IL-5-directed therapy. The use of validated symptom, endoscopic, and histologic endpoints substantiates IL-4- and IL-13-directed therapy efficacy. Preliminary results suggesting effectiveness in steroid refractory patients are intriguing, as such patients may prove to be ideal candidates for this type of treatment.

Conclusions

The scientific basis and clinical application of therapies targeting specific immunologic pathways in EoE and EGIDs are areas of active interest and growing relevance. An important subset of patients with EoE show limited response to topical steroids and elimination diet therapies, bringing an important unmet therapeutic need to light. Furthermore, the data are inconclusive regarding the long-term effectiveness and safety of topical steroids and diet therapies. For EGIDs, the use of systemic steroids present unacceptable long-term risks. Dietary therapy for both EoE and EGIDs adversely affect quality of life by necessitating avoidance of many commonly ingested table foods. Several of the biologic agents this review discusses target mechanisms common to multiple manifestations of atopy. Since patients with EoE and EGIDs typically manifest “extra-esophageal” and “extra-intestinal” forms of allergic disease, systemic therapy with a biologic offers potential advantages as a global treatment approach that could limit the need for multiple, locally active medical therapies and allergen avoidance. Of the agents that have been evaluated, biologics targeting IL-4 and IL-13 have demonstrated the most robust treatment benefits using validated outcome assessments. Ongoing clinical trials utilizing clinical outcome metrics and investigative work will hopefully lead to novel, effective, and safe biologic treatment strategies for gastrointestinal eosinophilic disorders that are increasingly recognized worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EoE	Eosinophilic Esophagitis
eos/hpf	eosinophils / high-power field
GERD	Gastroesophageal reflux disease
PPI	Proton pump inhibitor
mAb	monoclonal antibody
RDBPCT	Randomized, double blind, placebo-controlled trial

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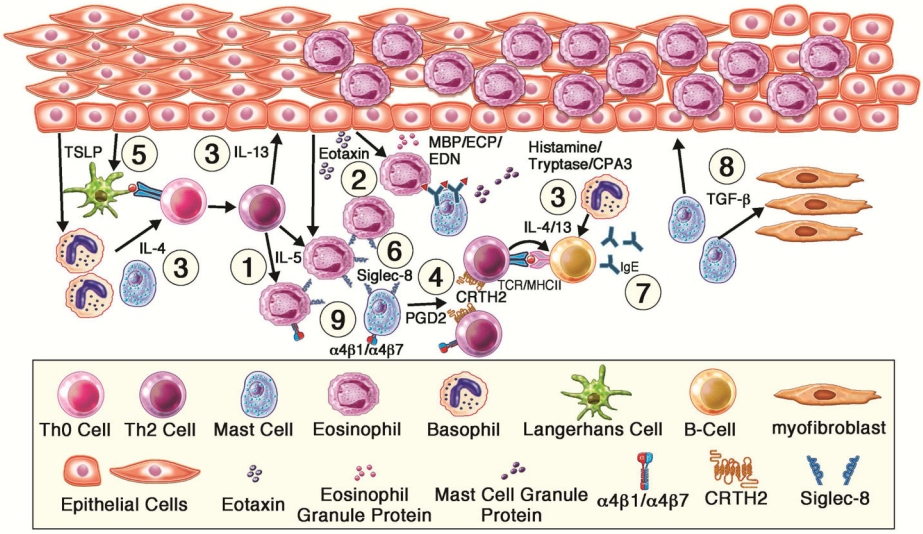

Figure.

Therapeutic targets for current and future biologics in eosinophilic esophagitis. Basophils and antigen-presenting cells mediate dietary antigen presentation to naïve T-cells (Th0), which through TSLP and IL-4 drives T-helper cell Type 2 (Th2) cell expansion. Th2 are recruited to the esophagus via integrins and prostaglandins and drive B-cell production of immunoglobulins, along with mast cell hyperplasia. Th2 cells secrete IL-5 which further enhances eosinophil recruitment via release of eotaxins and eosinophil survival. Th2 cells secrete IL-13, which dysregulates the epithelium to recruit Th2 inflammatory cells and promotes remodeling. Eosinophils and mast cells are effector cells that are activated to secrete proteases, cytokines and histamine which drive mucosal inflammatory changes and symptoms. TGF-β1 has a key role in fibrosis. Specific targets discussed include: 1) IL-5R, 2) Eotaxins, 3) IL4R/IL13, 4) CRTH2, 5) TSLP, 6) Siglec-8, 7) IgE, 8) TGF-β1, 9) Integrin $\alpha 4\beta 1/7$

Table 1

Targets of therapy, role in pathogenesis, and associated pharmaceuticals

Target	Role in pathogenesis	Clinical Trials in EGIDs	Clinical Trials (Atopic Disease)	Clinical Trials (non-Atopic Disease)
IL-5/IL5-R	**Activation and Recruitment of Eosinophils**	Mepolizumab, Reslizumab, Benralizumab	Mepolizumab, Reslizumab, Benralizumab	Mepolizumab
IL-13	**Promote eosinophil recruitments, barrier dysfunction, remodeling**	QAX576, RPC4046	Tralokinumab	Tralokinumab
IL-4RA	**Maintenance of Th2 inflammatory process**	Dupilumab	Dupilumab, AMG 317	
CRTH2	**Recruitment of T-cells**	OC000459	AZD1981, OC459, QAV680	
Siglec-8	**induction of eosinophil cell death inhibition of mast cell activation**	AK002	AK001, AK002	
TSLP	**Recruitment of basophils, stimulation of IL-4 to promote Th2**		Tezepelumab (AMG 157)	
Integrin alpha4beta7	**Recruitment of T-cells, eosinophils and mast cells**			Vedolizumab
Eotaxin-1, -2, -3	**Recruitment of eosinophils**		GW766994	
TGF-β1	**Enhance collagen production to promote fibrosis Promote smooth muscle contraction Worsen barrier integrity**	Losartan		Fresolimumab, Losartan

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