

EXPERT OPINION

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Emerging drugs for eosinophilic esophagitis

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Introduction: Eosinophilic esophagitis (EoE) has emerged over the past two decades as an important esophageal disorder with significant associated morbidity. The prevalence of EoE now approximates that of commonly recognized gastrointestinal diseases including inflammatory bowel disease. In adults, EoE is now a leading cause of dysphagia and food impaction. Medications, food elimination diets and esophageal dilation are currently utilized for the treatment of EoE. While these approaches are often effective, no pharmaceutical agents have yet been approved by the Food and Drug Administration (FDA). The current medical therapies for EoE primarily consist of topical corticosteroids that have been adopted from formulations designed for pulmonary delivery in patients with asthma and have not been optimized for esophageal delivery.

Areas covered: This article focuses on therapeutics being developed for EoE. Several trials have evaluated improved steroid vehicles designed for topical delivery to the esophagus. Novel biologic compounds, including anti-interleukin-5 and anti-interleukin-13, are being evaluated as targeted treatment options in EoE patients. Inhibitors of mast cell-derived prostaglandin D₂ (PGD₂) are also being studied, based on the concept that mast cells play an important role in EoE pathogenesis. Additional therapies, including immunomodulators, leukotriene antagonists, allergy immunotherapy and angiotensin II receptor blockers, are also examined in this article.

Expert opinion: No FDA-approved prescription medications are currently available for EoE patients. Although a number of novel agents are being developed and tested, Phase III clinical trials are scarce. Since EoE is a newly described disease, physicians have an incomplete understanding of the disease's pathogenesis, natural history and disease manifestations. This has led to significant difficulties in determining the most appropriate endpoints of therapy. Clinical trials are hampered by the lack of an accepted, standardized disease activity measure or biomarker by which therapeutic efficacy is assessed. Effective and approved pharmaceutical therapies are eagerly awaited by both physicians and patients for this increasingly recognized and clinically important disease.

Keywords: 6-MP, AZA, ciclesonide, CRTH2 antagonist, dysphagia, endoscopy, eosinophilic esophagitis, EoE, eotaxin-3, esophagitis, FP, gastroesophageal reflux disease, infliximab, IL-13, IL-5, leukotriene antagonist, mepolizumab, OC000459, omalizumab, OVB, QAX576, reslizumab, sirolimus, topical steroid

Expert Opin. Emerging Drugs [Early Online]

1. Background

Eosinophilic esophagitis (EoE) has emerged as one of the leading causes of upper gastrointestinal symptoms in both adults and children [1]. The etiology and pathogenesis of the disease are becoming better understood. The most recent

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consensus guidelines define EoE as a 'chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophilic-predominant inflammation' [2]. Whereas children often suffer from abdominal pain, nausea or vomiting, adults typically present with dysphagia. Food impaction requiring emergent endoscopic extraction is a common complication of EoE. Dysphagia is of concern as it significantly impacts quality of life and can cause patients to substantially modify their eating habits or minimize their eating in public [2,3]. Once considered rare, the incidence of EoE is estimated at 7.4 patients per 100,000 inhabitants in well-developed countries, and the prevalence of EoE is estimated at 43 patients per 100,000 inhabitants [4]. These incidence rates now approach those of inflammatory bowel disease and continue to increase [4]. Given the prevalence of EoE, studies have indicated that it is cost-effective to biopsy patients with upper gastrointestinal (GI) symptoms for EoE [5].

Current therapies for EoE utilized in clinical practice include steroids, dietary elimination and esophageal dilation [2]. As the medical community better delineates the pathways underlying the disease, targeted agents are being developed. Biologic agents, immunomodulators and leukotriene antagonists, as well as steroids with improved delivery to the esophageal mucosa, have emerged as promising therapeutic modalities.

2. Medical need

There is a great need for the development of therapeutics in EoE. No drugs are currently approved by the US Food and Drug Administration (FDA) [6]. Pharmacologic therapies for EoE offer the ability to reduce symptom burden and avert important adverse disease outcomes that include food impactions, esophageal strictures and impaired quality of life. Food impactions are a common initial presentation for adults with EoE. During these acute episodes, inability to pass an ingested food bolus from the esophagus frequently necessitates an emergency room visit with urgent endoscopic extraction of the bolus. Food impactions have been associated with major complications of severe chest pain and esophageal perforation that may require hospital admission and surgical intervention. Esophageal strictures are often managed endoscopically with esophageal dilation. As discussed below, dilation has also been associated with risks of both chest pain and esophageal perforation. In terms of quality of life, EoE has been associated with patient reported anxiety regarding impaired swallowing, social embarrassment created by choking in public and concerns of disease progression. Given these well-recognized disease complications and steadily rising disease prevalence, drug therapies are eagerly awaited [6].

The most readily utilized therapeutics in clinical practice today include off-label, topical or systemic steroids, dietary elimination and esophageal dilation. Orally administered, topical corticosteroids have demonstrated convincing efficacy

in the reduction of mucosal inflammation but less consistent improvement in the clinical symptoms in EoE. Systemic corticosteroids, while highly effective, have an unacceptable long-term side-effect profile [7,8]. As a consequence of the removal of common table foods, elimination diets, while highly effective in improving inflammation and symptoms, may adversely affect social functioning and emotional well-being. Reintroduction of foods for the purpose of identifying specific triggers subjects patients to costly repeated endoscopies [9].

3. Existing treatment

3.1 Topical steroids

The two most commonly used topical steroids are swallowed aerosolized fluticasone propionate (FP) and oral viscous budesonide (OVB). FP was the first studied topical agent for EoE and is administered via metered-dose inhaler (MDI) and then swallowed. Multiple randomized controlled trials (RCTs) have shown significant improvement in esophageal pathology following FP in both pediatric [10,11] and adult [12-14] patients. Similarly, an RCT of swallowed, nebulized budesonide demonstrated significant efficacy of the steroid over placebo [15]. Esophageal pathology improved with a reduction in eosinophilic inflammation from 62 to 6 eos/hpf per high-power field (eos/hpf) with only 15 days of budesonide 1 mg b.i.d. In this study, symptoms measured by a nonvalidated symptom assessment instrument significantly improved.

Given the challenge associated with the proper esophageal delivery of swallowing the aerosolized formulations of topical steroids, OVB was developed to improve the drug delivery. OVB is a mixture of aqueous budesonide and sucralose, and forms a readily swallowed suspension. In the initial pediatric RCT, 3 months of OVB resulted in a reduction in esophageal eosinophilia from 67 to 5 eos/hpf without appreciable change after placebo. Subsequent RCTs, in both adults and pediatrics, have demonstrated significant histologic improvement after OVB therapy [16-18]. One study to date directly compared nebulized budesonide with OVB and demonstrated superiority of the viscous formulation in decreasing esophageal eosinophilia [16].

Despite these advances, recent studies have demonstrated important limitations to both FP and OVB. A placebo-controlled study of FP in children demonstrated histologic remission, defined by the authors as < 1 eos/hpf, in only 50% of patients [11]. A similar trial of FP in adults noted that only 62% reached a complete histologic response, which was defined as $> 90\%$ decrease in mean eosinophil counts [13]. Seventy-one percent of patients in this study had < 5 eos/hpf after treatment. Moreover, symptom improvement was not statistically superior to placebo. Studies evaluating OVB have been more favorable, with $\sim 64\%$ of adults [16] and between 77 and 87% of children [17,18] attaining a complete histologic response. Significant symptom improvement was reported in both the pediatric and adult

studies with OVB that used nonvalidated patient-reported outcome instruments.

In addition to efficacy concerns for symptom resolution, FP and OVB are limited in other respects. First, although several dosing regimens have been proposed for both formulations, there is no consensus as to the most effective dose required for either induction or maintenance therapy [2]. Second, the relatively short duration with which these therapies have been used in EoE has precluded the accumulation of long-term safety data [2]. Indeed, rates of esophageal candidiasis, the most common side effect, have been estimated between 0 and 26% [13,19]. The majority of reported cases of esophageal candidiasis were asymptomatic and likely of limited clinical significance. Current studies have not demonstrated an association with adrenal insufficiency. Although the doses of topical steroids currently being used for EoE exceed those used for asthma, the lower bioavailability of these agents when delivered to the GI tract is expected to reduce the expected risks of systemic steroid-associated side effects.

3.2 Proton pump inhibitors

According to the most recent guidelines, the diagnosis of EoE incorporates a lack of a clinicopathologic response to proton pump inhibitor (PPI) treatment in an attempt to minimize the potential confounding of the diagnosis by gastroesophageal reflux disease (GERD) [2]. While pH testing may be helpful for the diagnosis of GERD, an abnormal test does not indicate a causal link between GERD and EoE. Patients who do respond to PPI therapy may have GERD or an entity referred to as PPI-responsive esophageal eosinophilia (PPI-REE) [2]. A therapeutic benefit of PPIs has recently been demonstrated in 30 – 50% of patients suspected of having EoE based on clinical presentation and esophageal eosinophilia. Recent studies have provided evidence that patients with PPI-REE have clinical, functional and molecular profiles that more closely resemble EoE than GERD [20]. *In vitro* data have demonstrated that PPIs inhibit the esophageal epithelial expression of eotaxin-3, an important eosinophil chemoattractant, identifying a potential acid-independent effect of PPIs on the esophageal eosinophilia underlying EoE [21].

3.3 Dietary modification

Dietary modification is another common treatment for EoE patients. Three dietary modification techniques predominate: i) the elemental diet, ii) the six-food elimination diet (SFED) and iii) an allergy testing-directed elimination diet [2,22]. The elemental diet is the most restrictive, limiting patients to the sole consumption of an amino acid-based formula. While extremely effective, the elemental diet is infrequently used because of the lack of palatability of the formulas, prolonged phase of reintroduction of table foods and expense when not covered by medical insurance [2]. Less restrictive than the elemental diet, the SFED eliminates the six most common food allergens from the diet (milk, wheat, egg, soy, seafood and nuts), and then systematically reintroduces them while

monitoring for relapse based on symptoms combined with repeated endoscopy with biopsy [9]. Although this approach can be effective in both children and adults, follow-up endoscopies are both costly and inconvenient, and dietary adherence requires substantial patient motivation and dietary monitoring [9]. Finally, the targeted approach relies on allergen testing to identify candidate foods for elimination. While less restrictive, it is also less effective than the elemental diet [2]. A high degree of both false-positive and false-negative allergy tests remains a significant problem that has impaired a widespread adoption of this particular form of diet therapy for EoE.

3.4 Dilation

Esophageal dilation therapy is a widely used and an effective treatment for the symptom of dysphagia in EoE patients. However, dilation therapy poses important risks. Of all patients who receive such therapy, as many as 70% experience postprocedural chest pain [2]. In most, the pain is mild or can be managed with mild analgesics. However, esophageal perforation has been reported. The risk of such events, based on a recent large series, approximates that for dilation of non-EoE benign esophageal strictures [2]. Furthermore, the perforations that have been reported in the context of esophageal dilation have been managed without surgical intervention. Conceptually more problematic is that dilation therapy does not address the underlying esophageal inflammation, which is believed to lead to long-term complications including esophageal remodeling and strictures [2].

4. Current research goals

Recent drug development has focused on improving the delivery of topical steroids to the esophageal mucosa. Novel anti-inflammatory and steroid-sparing immunomodulators, used in the treatment of other chronic inflammatory diseases, are also being investigated. More targeted biologic agents are also being developed as the mechanisms underlying EoE become better understood. Table 1 lists the therapeutic agents currently being evaluated.

5. Scientific rationale and competitive environment

5.1 Topical steroids

5.1.1 Rationale

Existing studies reviewed earlier with off-label use of topical corticosteroids have demonstrated efficacy in terms of histopathology with variable responsiveness in terms of symptoms. Researchers are pursuing improved delivery methods to concentrate the steroids in the esophagus while minimizing potential systemic side effects. Although few studies have examined the long-term safety of topical steroids, the risk of systemic side effects from long-term corticosteroid exposure represents an area of concern for both patients and providers.

Table 1. Competitive environment.

Compound (chemical class when appropriate)	Company or sponsor	Indication	Study type (National Clinical Trials Identifier if available)	Study phase	Mechanism of action
<i>Topical steroids</i>					
Ciclesonide	None	EoE	Investigator initiated	No clinical trials submitted	Converts to des-CIC in the esophagus and activates local glucocorticoid receptors
Fluticasone	None	EoE	Investigator initiated	Investigator initiated randomized controlled trial completed	Aerosolized steroid that is swallowed for esophageal delivery
Orodispersible budesonide	Falk Pharma	EoE	Investigator initiated	No clinical trials submitted	Improved esophageal delivery of topical steroid
Oral Budesonide Suspension	Meritage Pharma, Inc.	EoE	Phase II (NCT01642212)	Recruiting subjects	Improved esophageal delivery of topical steroid
<i>Immunomodulators</i>					
AZA	None	Steroid-dependent or steroid-refractory EoE	Investigator initiated	No clinical trials submitted	Th2 leukocyte inhibition
6-MP	None	Steroid-dependent or steroid-refractory EoE	Investigator initiated	No clinical trials submitted	Th2 leukocyte inhibition
Sirolimus	National Institute of Allergy and Infectious Diseases (NIAID)	Steroid-dependent or steroid-refractory EoE	Phase I (NCT01814059)	Recruiting subjects	Th2 leukocyte inhibition
<i>Biologics</i>					
Reslizumab	Ception Therapeutics	EoE	Phase II/III (NCT00538434) Phase III (NCT00635089)	Completed, Results published Completed, Results unpublished	Monoclonal antibody against IL-5
Mepolizumab	GlaxoSmithKline	EoE	Phase II (NCT00274703) Phase II (NCT00358449)	Completed, Results published Completed, Results published	Monoclonal antibody against IL-5
QAX576	Novartis Pharmaceuticals	EoE	Phase II (NCT01022970)	Completed, Results unpublished	Monoclonal antibody against IL-13
RPC4046	Receptos	EoE	Phase II planned	Not yet recruiting	Antibody against IL-13
Omalizumab	Novartis Pharmaceuticals Genentech	EoE	Phase II (NCT00123630) Phase I (NCT01040598)	Completed, Results published Completed, Results unpublished	Monoclonal antibody against IgE
Infliximab	None	Steroid dependent or refractory EoE	Phase II (NCT00523354)	Completed, Results published	Monoclonal antibody against TNF- α
OC000459	Oxagen Ltd	EoE	Phase II (NCT01056783)	Completed, Results published	CRTH2 antagonist
<i>Miscellaneous</i>					
Montelukast (leukotriene receptor antagonist)	Merck	EoE	Phase I (NCT00511316) Phase III (NCT01702701)	Recruiting subjects Active, not recruiting subjects	Inhibition of eosinophil chemotaxis
	None		Phase unpublished (NCT01458418)	Not yet recruiting subjects	
Allergy immunotherapy	None		Phase unpublished (NCT01685034)	Not yet recruiting subjects	Allergen sensitization
Losartan (angiotensin II receptor blocker)	None		Phase II (NCT01808196)	Recruiting subjects	Inhibition of TGF- β signaling

CRTH2: Chemoattractant receptor-homologous molecule on Th2 cells; EoE: Eosinophilic esophagitis; IL: Interleukin-5; IgE: Immunoglobulin E; Th2: T-helper type 2; TNF- α : Tumor necrosis factor-alpha; TGF- β 1: Transforming growth factor- β 1.

5.1.2 Competitive environment

5.1.2.1 Ciclesonide

One topical steroid receiving recent attention is ciclesonide, an inhaled corticosteroid used for asthma and allergic rhinitis. Ciclesonide is rapidly hydrolyzed into the active compound desisobutyryl-ciclesonide (des-CIC) [23]. Ciclesonide, and by extension des-CIC, possesses two pharmacologic properties that make it particularly appealing in the context of EoE therapy. First, des-CIC binds with 100 times the affinity of budesonide to the esophageal glucocorticoid receptors, potentially offering greater local efficacy [24]. Second, the drug is rapidly metabolized by the liver or bound to serum proteins, thus minimizing systemic effects [23-25]. Studies in asthmatic patients comparing ciclesonide against budesonide or fluticasone have demonstrated somewhat reduced adverse effects [26-28].

Only two published studies with small patient cohorts have examined the application of ciclesonide to EoE patients (Table 1) [29,30]. Schroeder and colleagues studied ciclesonide in four children, all of whom showed statistically significant histologic improvement as well as symptom resolution after 2 months of ciclesonide therapy [29]. Lee and colleagues also studied four children using ciclesonide, although the study demonstrated less conclusive improvement [30]. In explaining their findings, Lee and colleagues theorize that the nonresponsive patients may have been steroid resistant as they had previously failed treatment with other topical steroids [30]. Given the limitations of these studies, and mixed findings, additional trials are needed to determine ciclesonide's potential in the treatment of EoE.

5.1.2.2 Fluticasone propionate

Initial prospective RCTs of off-label use of existing asthma formulations of FP have demonstrated significant improvement in esophageal eosinophilia after treatment. Published studies have utilized the aerosolized formulations of FP with patients instructed to swallow rather than inhale the medication. Improved vehicles of FP optimized for esophageal delivery are needed. An extensive first-pass hepatic metabolism of FP improves its safety margin by reducing the potential for systemic side effects.

5.1.2.3 Oral budesonide

Given the promising results of earlier OVB trials in both children and adults with EoE, a large, Phase II randomized, double-blind, placebo-controlled study is being conducted to better characterize both histologic and symptomatic improvements with an oral budesonide suspension [31]. Sublingually dissolving budesonide tablets are also being evaluated in EoE patients [32,33].

5.2 Immunomodulators

5.2.1 Rationale

Studies have demonstrated that the vast majority of patients with EoE develop recurrent disease activity after cessation of topical corticosteroids. Although topical steroids represent a

first-line treatment, some patients require systemic steroids to control their disease. A small subset of patients may be steroid refractory [34]. Given the toxicity associated with long-term steroid use, steroid-sparing agents such as azathioprine (AZA), 6-mercaptopurine (6-MP) and sirolimus have been proposed for use in EoE [34,35].

AZA is a prodrug that gets metabolized into 6-MP, a purine inhibitor. In addition to impairing DNA and RNA synthesis, AZA/6-MP also decreases B- and T-lymphocyte proliferation [34]. It has been postulated that EoE is a T-helper type 2 (Th2) lymphocyte-mediated process, by which Th2 lymphocytes proliferate and release inflammatory cytokines (Figure 1) [34,36]. It is believed that immunomodulatory drugs may offer relief since they act to decrease inflammation by impeding esophageal lymphocyte recruitment.

5.2.2 Competitive environment

5.2.2.1 AZA and 6-MP

One case series to date, involving three steroid-dependent adults with EoE, evaluated AZA/6-MP for maintaining disease remission in EoE [34]. Two were started on AZA, and one was given 6-MP due to nausea from AZA [34]. All three maintained histologic remission with the immunomodulators and were successfully weaned off steroids. However, when the immunomodulators were eventually withdrawn, all three patients relapsed. Therefore, it is postulated that ongoing immunosuppressive therapy was necessary to maintain disease control [34]. Further studies are necessary to understand the role of immunomodulatory drugs in severe or steroid refractory EoE.

5.2.2.2 Sirolimus

Outside of the EoE context, sirolimus is an immunomodulator commonly used in transplant patients to prevent rejection [35]. As the agent inhibits Th2 cell proliferation *in vitro*, sirolimus might play a role in the treatment of EoE. A Phase I open-label study of sirolimus in EoE is currently recruiting patients [35].

5.3 Biologics

5.3.1 Rationale

Biologic agents represent a promising class of emerging therapies that target specific pathways believed to be critical to the pathogenesis of EoE, especially the Th2 pathway [37]. The Th2 pathway is mediated by three key cytokines: interleukin (IL)-4, IL-5 and IL-13 [37]. IL-4 increases differentiation of naïve T-helper cells into Th2 cells and promotes eosinophil chemotaxis [37,38]. IL-5 acts on the bone marrow to induce eosinophil maturation and migration into circulating blood and tissue, including the esophagus [39,40]. IL-5 additionally activates eosinophils, promoting degranulation, and augments B-cell-mediated immunoglobulin E (IgE) release [38]. In the esophagus, IL-13 induces esophageal keratinocytes to increase gene transcription of eotaxin-3, a potent eosinophil chemoattractant [41-43]. IL-13 secretion may also disrupt the esophageal

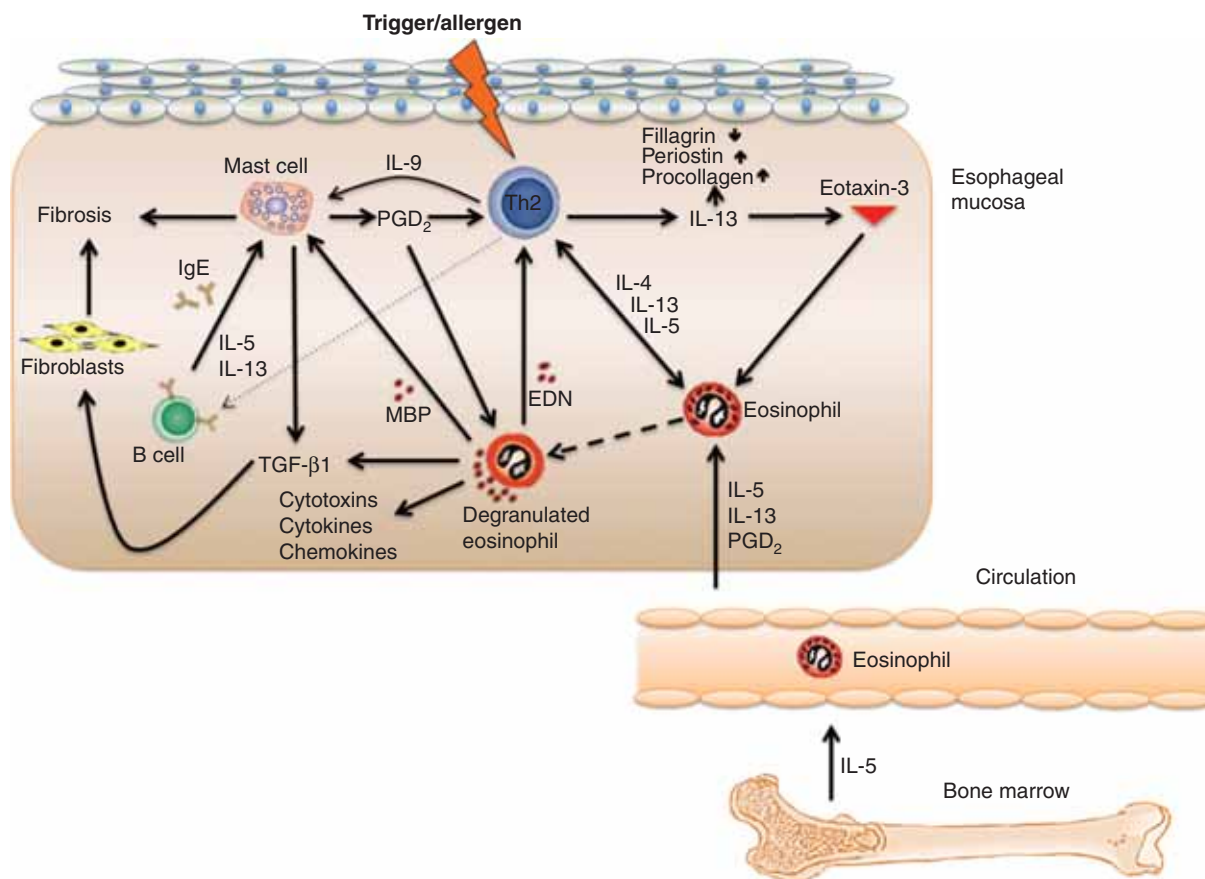


Figure 1. Mechanism of EoE pathogenesis highlighting therapeutic targets. Triggers, including food and possibly aeroallergens, activate Th2 cells, which release IL-13, IL-4 and IL-5. IL-13 induces esophageal epithelial cells to express eotaxin-3, an eosinophil chemoattractant. IL-13 also affects the esophageal epithelial barrier by upregulating periostin and downregulating filaggrin. Activated eosinophils release cytotoxic granules, including MBP and eosinophil-derived neurotoxin (EDN). MBP, along with B-cell-associated IgE, activates mast cells, which release PGD₂. PGD₂ binds to the receptors on Th2 lymphocytes and eosinophils, promoting both chemotaxis and activation. EDN also induces Th2 polarization, thus further propagating the inflammatory cycle. TGF-β released by activated eosinophils induces fibrosis.

epithelial barrier and potentially promote fibrosis via upregulation of procollagen and periostin [42-44]. Finally, IL-13 acts on B cells to promote IgE production [38].

While Th2 lymphocytes are central to EoE pathogenesis, at least three other cell types are also significantly implicated, including eosinophils, mast cells and esophageal keratinocytes [37,45]. Eosinophils, once activated, release proinflammatory cytokines, profibrotic agents and cytotoxic granules [36,41]. Eosinophils are also thought to release transforming growth factor-β1 (TGF-β1), an inflammatory cytokine that contributes to fibrosis [41].

Mast cells are also an important contributing cell type in the EoE pathway. Mast cells are activated by a number of factors, including IgE from B lymphocytes and major basic protein (MBP) from eosinophils [43]. In addition to releasing TGF-β1, activated mast cells release prostaglandin D₂ (PGD₂) [41,46]. PGD₂ binds to the DP2 receptor, also known as the chemoattractant receptor-homologous molecule on

Th2 cells (CRTH2) [46]. When PGD₂ binds to the CRTH2 receptor on Th2 lymphocytes and eosinophils, it promotes both chemotaxis and activation, and thus furthers the inflammatory cascade [46]. The CRTH2 receptor has been targeted in a number of studies involving this pathway [45,46].

5.3.2 Competitive environment

5.3.2.1 Anti-IL-5 antibodies

5.3.2.1.1 Reslizumab and mepolizumab

Reslizumab and mepolizumab, monoclonal antibodies against IL-5, have been studied for use in EoE [1]. Three published RCTs to date, which included both adults and children, have examined these agents [39,47,48]. In each of these trials, patients experienced a significant reduction in esophageal eosinophils, although most did not reach histologic resolution [7,48]. Reductions in eosinophils notwithstanding, many patients did not experience a statistically significant symptomatic improvement compared to the placebo [39,47]. Whether

this was due to difficulties with symptom measurement, insufficient treatment duration or limited efficacy is unclear [39]. At present, neither reslizumab nor mepolizumab is currently available for clinical use. A Phase III study of reslizumab investigating longer term safety and efficacy has been completed with results pending [49].

5.3.2.2 Anti-IL-13 antibodies

5.3.2.2.1 QAX576

Although a number of anti-IL-13 antibodies have been developed, the application of these antibodies has generally been limited to asthma, allergic rhinitis or inflammatory bowel disease [42]. Only one trial has currently evaluated an anti-IL-13 antibody, QAX576, in EoE patients [50]. The results of this Phase II RCT, which randomized 25 adults with EoE to either 12 weeks of QAX576 or placebo, have not yet been reported [50].

5.3.2.3 Anti-eotaxin-3 antibodies

Given that EoE involves the movement of eosinophils to the esophagus, agents that block such movement are potentially effective therapies. Eotaxin-3 is the most highly induced gene on the basis of genome-wide mRNA expression analysis and implicated in trafficking eosinophils to the esophagus in EoE [38]. EoE patients may even have a genetic defect, making them particularly susceptible to eosinophilia promoted by eotaxin-3 [38,51]. It has been postulated that certain therapeutic agents may downregulate the production of eotaxin-3 in EoE [21]. No anti-eotaxin-3 antibodies have been studied in EoE patients [2].

5.3.2.4 Anti-IgE antibodies

5.3.2.4.1 Omalizumab

Omalizumab is a monoclonal anti-IgE antibody that has been extensively used in patients with allergic asthma [1]. Only one published RCT to date examined the application of omalizumab to EoE [52]. This study, which enrolled 30 adults with EoE, found no benefit in either clinical symptoms or histology after four treatments with omalizumab [52]. A Phase I trial to identify mucosal markers of omalizumab responders has been completed with results pending [53].

5.3.2.5 Anti-tumor necrosis factor- α antibodies

5.3.2.5.1 Infliximab

Infliximab is a monoclonal antibody to tumor necrosis factor- α (TNF- α) that is often used in rheumatoid arthritis and Crohn's disease [54]. Mast cells release TNF- α upon degranulation [43]. One prospective, open-label trial investigated the role of infliximab in three adult males with corticosteroid-dependent EoE [54]. The results indicated that infliximab provided neither symptomatic improvement nor histologic resolution [54]. No additional clinical trials of anti-TNF therapy in EoE are currently under way.

5.3.2.6 CRTH2 antagonists

5.3.2.6.1 OC000459

OC000459 is a selective CHRT2 antagonist that has been studied in eosinophilic asthma [46]. OC000459 is believed to block the effects of PGD₂ on eosinophils and Th2 lymphocytes [45]. A small RCT has investigated the role of OC000459 in patients with steroid-dependent or steroid-refractory EoE [45]. OC000459 induced a significant decrease in esophageal eosinophilia and showed a trend toward improvement in endoscopic abnormalities compared to placebo [45]. Further trials are needed to clarify the efficacy and safety of OC000459.

5.4 Leukotriene receptor antagonists

5.4.1 Rationale

Another emerging therapeutic approach is the use of leukotriene receptor antagonists in EoE. Leukotriene D₄ is a known eosinophil chemoattractant [55]. Antagonists to the leukotriene D₄ receptor are being studied as a possible therapeutic target in EoE [55]. These drugs have already been established in other atopic diseases such as asthma [55]. By inhibiting eosinophil chemotaxis, leukotriene antagonists may interfere with the underlying disease mechanism.

5.4.2 Competitive environment

5.4.2.1 Montelukast

Montelukast is a leukotriene D₄ receptor antagonist used in asthmatic patients [55]. An initial, open-label trial of montelukast in eight adult EoE patients demonstrated symptomatic relief with the drug [56]. However, montelukast failed to maintain a corticosteroid-induced histologic remission in these patients. Furthermore, in additional studies in both pediatric [57] and adult [55] populations, montelukast did not induce a clinical or histologic response. Some experts have subsequently queried whether the dosages used in these studies were adequate [55,58]. A Phase I RCT evaluating the use of higher doses of montelukast for maintaining histologic remission induced by topical steroids is currently recruiting participants [59]. A larger Phase III RCT comparing montelukast to fluticasone is also ongoing [60]. In addition, an RCT investigating whether a chewable form of the drug is more effective has been proposed but is not yet open for recruitment [61].

5.5 Allergy immunotherapy

5.5.1 Rationale

Allergy immunotherapy (AIT) has been hypothesized to be another possible therapy because of the association between EoE and other allergic diseases [62]. EoE is an antigen-driven allergic disease, and most EoE patients have a significant personal history of atopy [2]. Current consensus guidelines suggest that EoE patients undergo an evaluation by an allergist for the optimal management of the atopic aspects of EoE as well as concomitant extra-esophageal allergic conditions.

5.5.2 Competitive environment

Several observational studies have reported an association between the clinical activity of EoE and the seasons, suggesting a role for aeroallergen activation of disease. More recent and larger studies, however, have not confirmed this association. A pilot study of aeroallergen immunotherapy in patients with both EoE and aeroallergen sensitivity, as demonstrated by skin prick testing, has been proposed [62]. Patients will be evaluated on histologic, symptomatic and endoscopic response 1 year after starting AIT. To date, subjects have not yet been recruited.

5.6 Angiotensin II receptor blockers

5.6.1 Rationale

Angiotensin II receptor blockers (ARBs) inhibit TGF- β , a key mediator believed to be involved in the EoE pathway. ARBs have previously been studied in connective tissue diseases with excessive TGF- β production, such as Marfan's syndrome [63]. It has been hypothesized that ARBs may inhibit the eosinophil and mast cell-mediated fibroblast activation associated with EoE (Figure 1) [64]. Studies demonstrating the esophageal expression of TGF- β in both children and adults with EoE combined with the well-defined role for TGF- β in fibrogenesis make this pathway an attractive therapeutic target.

5.6.2 Competitive environment

5.6.2.1 Losartan

A Phase II, double-blinded RCT involving losartan is currently recruiting pediatric EoE patients [64]. Patients will be started on low doses of losartan and up-titrated as tolerated. The study will evaluate patient response via histologic, endoscopic and symptomatic improvement. TGF- β levels will also be measured before and after treatment [64].

6. Potential development issues

There are a number of factors that presently hamper the development of novel EoE therapies [23-30,65,66,31-64]. First and foremost, the definition of therapeutic success in the context of EoE has not been established [6,67]. Histopathologic, endoscopic and symptomatic outcomes have each been proposed as targets by which to assess the efficacy of EoE therapies is assessed [67]. Each of these targets, however, is complicated by one or more limitations.

The use of tissue eosinophilia has both conceptual and practical drawbacks. While esophageal eosinophilic inflammation is an accepted diagnostic criterion for EoE, studies have demonstrated limited correlation between the degree of esophageal eosinophilia and patients' symptom severity. Furthermore, the eosinophilic inflammation of EoE is associated with substantial esophageal mural remodeling with subepithelial fibrosis and transmural esophageal thickening that is not adequately assessed with mucosal biopsies. Therefore, it is unclear that histopathologic resolution is the most important therapeutic outcome in terms of patients' overall disease

activity, which is a composite of both inflammation and tissue remodeling. In spite of these limitations, esophageal eosinophilia has remained the most widely utilized determinant of inflammatory disease activity. In this regard, controversy has surrounded the appropriate threshold of esophageal eosinophilia that defines successful response [67]. Thresholds of < 5 , < 10 and < 15 eos/hpf as well as a percentage reduction of baseline eosinophilia have been used by different investigators. Additional histologic parameters of esophageal inflammation including basal cell hyperplasia, mast cell concentrations, subepithelial fibrosis and eosinophil degranulation have been examined as determinants of response.

Endoscopically identified esophageal features are a potentially important therapeutic endpoint as they incorporate both inflammatory (edema, furrows, exudates) as well as remodeling (rings, strictures) features of EoE. Inclusion of remodeling consequences of EoE in the assessment of disease activity may account for the increasingly appreciated discrepancy between symptom and histologic severity. Recently, a classification and grading system characterizing the major endoscopic features of EoE was validated [68]. Further studies have shown a correlation between the severity of esophageal fibrostenotic features on endoscopy and the risk of food impaction [69]. Importantly, in this same study, esophageal eosinophilia was not a significant determinant of food impaction risk. Interestingly, clinical trials in inflammatory bowel disease have shifted attention to the importance of endoscopically assessed mucosal healing as a primary determinant of therapeutic success. Whether this same paradigm applies to EoE is uncertain. Additional potential targets for monitoring disease activity including biomarkers, subepithelial fibrosis and esophageal distensibility are actively being investigated [70,71].

Several studies have highlighted the important dissociation between symptomatic and histologic activity in EoE [16,17,69,70,72]. Difficulties in symptom assessment include the variation of symptoms between afflicted children and adults, the intermittent nature of symptoms and the ability of symptoms to improve as the result of dietary modification. Moreover, symptoms reflect a composite of both inflammatory and remodeling effects of EoE activity. Current pharmacologic therapies for EoE are focused on the inflammatory aspects of disease. Detection of significant symptom improvement that is dominated by the remodeling effects of EoE may be more challenging. Finally, improvement in symptom-based patient-reported outcomes currently does not account for quality-of-life issues implicated by EoE [67,72].

Another important issue pertinent to the development of therapeutics for EoE is disease heterogeneity [73]. Children with EoE clearly present in a different manner, both symptomatically and endoscopically, as compared with adults. Most of these differences are conceptually explained by the contribution of variable degrees of tissue remodeling. Subtypes of EoE may present with a more allergic phenotype and demonstrate variable responses to treatment with topical corticosteroids. Additional studies have demonstrated genetic

determinants of steroid nonresponse in EoE including FKBP51, microRNA675 and the TGF- β 1 promoter. As research in EoE continues, a better understanding of these phenotypic and genotypic determinants of therapeutic response is necessary [74-76].

7. Conclusion

EoE is a chronic inflammatory disease of the esophagus that significantly impacts both pediatric and adult patients with rapidly increasing prevalence worldwide. Current treatment options include suppressing inflammation with immunosuppressants, avoiding inflammatory triggers with restrictive diets and managing the fibrostenotic consequences of disease with esophageal dilation. While each of these treatment options poses therapeutic benefits, they each come with inherent limitations.

Novel therapeutic agents that target the underlying disease process are currently in development. These include topical steroids optimized for esophageal delivery, steroid-sparing immunosuppressants and novel biologic agents specifically designed to disrupt signaling pathways in EoE. Although a number of these novel biologic agents offer great potential, RCTs establishing efficacy and safety are limited. Furthermore, none are currently available in clinical practice. Optimal disease biomarkers and therapeutic endpoints are critical to allow for the development of effective therapies for EoE.

8. Expert opinion

EoE has emerged as an important and increasingly common cause of substantial morbidity in both children and adults. The disease impacts patients' nutritional well-being and quality of life, and has been associated with significant complications including food impaction and esophageal perforation. Financial costs associated with EoE include emergency room visits for food impaction, repeated upper endoscopy with esophageal dilation, allergen free diets and thoracic surgery for esophageal rupture, albeit rare. EoE therapies are rapidly evolving as the mechanisms underlying the disease become better understood. Most drugs are in the early stages of development; none are currently available for patients outside of clinical trials. At this time, the most significant therapeutic efficacy has been demonstrated with the use of topical, swallowed corticosteroids. The agents currently being studied, fluticasone and budesonide, are already in clinical use for allergic and chronic inflammatory conditions such as asthma, allergic rhinitis and inflammatory bowel disease. The benefits of these agents have been convincing in terms of tissue inflammation. Symptom benefits have been more difficult to demonstrate, possibly due to limitations in available patient-reported outcome instruments as well as symptom-pathology dissociation related to esophageal remodeling.

While corticosteroids are a frontline therapy for EoE children and adults, increasingly recognized are a subgroup of

EoE patients who are either refractory or chronically dependent upon topical corticosteroids. Studies involving therapies targeting specific immunologic targets in the pathogenesis of EoE offer great promise but currently have demonstrated significant but modest histologic improvement. Potential benefits of this approach include avoidance of long-term corticosteroids and ability to act as disease-modifying agents. Conceptually, systemically acting therapeutic agents may offer greater disease benefits than topically acting agents. Although IL-5 is mechanistically positioned as a key cytokine in the pathogenesis of EoE, the limited therapeutic effects of anti-IL-5 agents, reslizumab and mepolizumab, provide evidence for multiple overlapping and interrelated pathways underlying EoE. The results of studies on anti-IL-13 therapy have not yet been reported. CRTH2 antagonists such as OC000459 are a new and highly promising therapeutic class. CRTH2 antagonists inhibit three major cell lines hypothesized to be central to EoE pathogenesis. The one trial that evaluated the efficacy OC000459 in the treatment of adults with EoE reported modest efficacy in terms of histologic response.

In the absence of an accepted, clinically meaningful endpoint for clinical trials in EoE, patient-reported symptom outcomes are currently emphasized as a primary measure of therapeutic success. The overwhelming symptom burden for adult patients with EoE is dysphagia that has been associated with inflammation and, more recently, tissue remodeling. The primary outcome for inflammation has been a reduction in the degree of esophageal eosinophilia. Therapeutics under development for EoE that target inflammatory pathways have less clear short-term benefits in terms of reversing pre-existing remodeling consequences. It may, therefore, be inappropriate to expect short-term use of anti-inflammatory agents to adequately address the fibrostenotic complications of EoE. To emphasize this point, the most rapidly effective treatment for dysphagia in adults with EoE is endoscopically guided, esophageal dilation. Relief of dysphagia is immediate and associated with significant patient-reported satisfaction [77]. Dilation, however, does not address the underlying inflammatory process responsible for the development of the stenosis. Reduction in esophageal inflammation rather than symptom relief may, therefore, be a more appropriate primary endpoint of the therapeutics currently in development. While this paradigm is yet unproven, the current emphasis on symptom outcomes recognizes the contribution of remodeling effects but potentially deemphasizes anti-inflammatory benefits. Utilization of the most accurate therapeutic endpoints is essential to avoid overlooking valuable treatments for this important and growing disease.

Declaration of interest

I. Hirano has served as a consultant for Meritage Pharma, Novartis, Receptos, Pfizer and Aptalis. E. kern has no conflict of interest.

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