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REVIEW

Recent discoveries and emerging therapeutics in eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is an allergy-mediated disease culminating in severe eosinophilic inflammation and dysfunction of the esophagus. This chronic disorder of the esophagus causes significant morbidity, poor quality of life, and complications involving fibrosis and esophageal remodeling. Overlapping features between EoE and gastroesophageal reflux disease (GERD) pose great challenges to differentiating the two conditions, although the two disorders are not mutually exclusive. Recent findings suggest that the confounding condition proton pump inhibitor - responsive esophageal eosinophilia (PPI-REE) is likely a subset of EoE. Since PPIs have therapeutic properties that can benefit EoE, PPIs should be considered as a therapeutic option for EoE rather than a diagnostic screen to differentiate GERD, PPI-REE, and EoE. Other current treatments include dietary therapy, corticosteroids, and dilation. Immunomodulators and biologic agents might have therapeutic value, and larger trials are needed to assess efficacy and safety. Understanding the pathophysiology of EoE is critical to the development of novel therapeutics.

Key words: Eosinophilic esophagitis; Interleukin-5; Proton pump inhibitors; Proton pump inhibitor-responsive esophageal eosinophilia; Gastroesophageal reflux disease; Eotaxin-3

Core tip: In this review, we will discuss recent challenges and discoveries in eosinophilic esophagitis (EoE). While current treatment options are limited, mainly dietary therapy and steroids, we will highlight emerging therapeutics targeting pathogenic mechanisms of the

disease. Although EoE is an allergy-mediated disease, the overlapping features of EoE and gastroesophageal reflux disease (GERD) present a diagnostic quandary in distinguishing the two disorders. EoE and GERD are not mutually exclusive and might share a complex relationship. We will review how proton pump inhibitor (PPI)s might exert therapeutic effects in EoE, and why a PPI response does not provide clear diagnostic distinction between EoE and GERD.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is allergy-mediated clinicopathologic entity in which eosinophils infiltrate into the esophagus resulting in esophageal inflammation, fibrosis and dysfunction[1]. EoE commonly causes symptoms of heartburn and dysphagia, and if left untreated, will likely progress to esophageal remodeling and stricture formation[2,3]. EoE was first recognized almost 20 years ago as a distinct entity[4,5]. Since several clinical and histological features of gastroesophageal reflux disease (GERD) and EoE overlap, patients with esophageal eosinophilia consistent with EoE were often diagnosed as GERD prior to recognizing EoE as a distinct entity[6]. EoE is relatively a newly recognized disease. Much of EoE pathophysiology is unclear, and several research efforts are dedicated to elucidating the relationships between host immune system, environmental factors, and genetic factors. Understanding and identifying pathogenic targets may lead to therapeutic advances. Currently, only off-label use of drugs and therapies are available for the treatment and management of EoE. Each therapy has benefits and challenges. Several therapies, including immunomodulators and biologic agents, will need further studies to determine safety and efficacy. In this review, we will discuss challenges in EoE diagnosis, new discoveries in pathophysiology, and emerging therapeutics.

EOE CLINICAL FEATURES AND DIAGNOSIS

EoE is a clinicopathologic disorder that requires both clinical and/or endoscopic features of esophageal dysfunction and histologic features of esophageal eosinophilia. EoE in children generally causes symptoms of nausea, emesis, abdominal pain, and failure to thrive. Adolescents and adults are more likely to present with dysphagia, food impaction, heartburn, and strictures[1]. The esophageal tissue remodeling rising from unabated inflammation has profound impact on disease activity such as dysphagia and stricture formation[7,8].

The endoscopic findings include white mucosal plaques, linear furrowing, esophageal trachealization (concentric rings), esophageal narrowing, stricture and mucosal tearing[3]. However, the endoscopic features alone are not sufficient to confirm diagnosis of EoE[9]. It is estimated that 10% of adults with EoE have normal endoscopy results[10]. The EoE endoscopic reference score EREFS is a new classification system recently developed to describe endoscopic findings and disease severity in patients with EoE[11]. The EREFS scores endoscopic features of EoE (exudates, rings, edema, furrows, and strictures) providing a validated outcome measure that will be critical in upcoming clinical trials.

The current consensus guidelines for diagnosis of EoE recommend $\geqslant$ 15 eosinophils per high-power field on at least one esophageal biopsy specimen, without increase in eosinophils in stomach and duodenum[1]. Biopsy specimens should be obtained from both the proximal and distal aspects of the esophagus during diagnostic and surveillance endoscopy[1]. Proper tissue sampling from the esophagus is a current challenge. EoE is a transmural disease involving all layers of the esophagus, however mucosal pinch biopsies often only attains the superficial epithelial layer. In addition, eosinophilic infiltration can be patchy, so biopsy collected from one site may not be sufficient for diagnosis[12]. Thus, current guidelines suggest taking 2-4 biopsies from the proximal and distal esophagus[13]. However, Nielsen *et al*[14] recently examined biopsy fragments in 102 adult EoE cases and determined that a minimum of 4 biopsy fragments from the mid and/or proximal esophagus submitted in separate containers would optimize diagnostic yield for EoE.

The main diagnostic conundrum is distinguishing EoE from GERD. However, GERD and EoE are not mutually exclusive disorders, and might share a complex relationship[15]. Firstly, GERD can have mild esophageal eosinophilia. Reflux-induced inflammation can involve eosinophil trafficking. Secondly, EoE might predispose to GERD. EoE inflammation and remodeling conceivably can alter esophageal motility, delay acid reflux clearance, and compromise the lower esophageal sphincter. Disrupted barrier function and increased permeability due to EoE inflammation might leave the epithelium hypersensitive to acid reflux injury as described in EoE patients[16]. Alternatively, GERD might perpetuate EoE. Gastric reflux induces mediators in the epithelium that can exacerbate activation of immune cells that promote allergic inflammation[17]. Disrupted barrier function due to acid-related injury might increase mucosal permeability to allergic antigens perpetuating allergic inflammation.

Early experts proposed using a PPI trial to dis-

tinguish GERD from EoE, assuming that PPIs only exert antisecretory, acid-suppressive effects, and therefore only GERD can respond to PPIs[18]. However, this assumption was called into question as reports of patients with PPI-responsive esophageal eosinophilia (PPI-REE) emerged[1,19-22]. PPI-REE patients have clinical, endoscopic, and histological findings consistent with EoE yet achieve clinical and histologic remission after PPI therapy. Prospective studies estimated that 33%-74% of patients with esophageal eosinophilia respond to PPI therapy[19-22]. Furthermore, there are multiple mechanisms whereby EoE patients might benefit from, not only acid-suppressive effects, but also anti-inflammatory effects of PPIs, as discussed later in this review[15]. Lastly, recent genetic transcriptome analysis of PPI-REE patients and EoE patients revealed remarkable molecular signature overlap suggesting that PPI-REE might indeed be a subset of EoE or represent a similar allergy-mediated process that responds to PPI effects[23].

EOE PATHOPHYSIOLOGY OVERVIEW

An understanding of EoE pathophysiology is essential in order to identify therapeutic targets and develop treatment options for the disease. The pathophysiology of EoE seems to involve disturbances in allergen exposures, the epithelial barrier, immune effector cells, and inflammatory cytokines. Current and investigational therapies are directed to these areas. In EoE, allergen (food and/or aeroallergens) permeate the epithelial barrier and initiate a T-helper type 2 (Th2) inflammatory reaction where activated Th2 lymphocytes increase tissue levels of Th2 cytokines, such as interleukin (IL)-5, IL-13, and IL-4[24,25]. These Th2 cytokines are responsible for driving eosinophil recruitment and activation. Eotaxin-3 is a potent eosinophil chemoattractant, highly regulated by Th2 cytokines IL-13 and IL-4, and is a signature gene for EoE[26]. Upon activation, eosinophils can secrete a variety of pro-inflammatory cytokines and chemokines or degranulate, releasing preformed granules containing cationic and cytotoxic proteins that are injurious to the tissue. While EoE involves an eosinophil-predominant inflammation, there is evidence to suggest that other immune cells, such as mast cells, basophils, and invariant natural killer T cells also mediate inflammation[27]. The ongoing chronic inflammation drives fibrogenesis and remodeling in the deeper layers of esophagus[8,28]. Next, we will highlight current and investigational therapies, therapeutic targets, and their relationship to EoE pathophysiology.

TARGETING ALLERGENS

Diet

First and foremost, EoE is an allergy-driven disease. A definitive link between EoE and food allergens was recognized after children with EoE achieved disease remission on an elemental diet and subsequently disease recrudescence following food reintroduction[29]. Therefore, dietary avoidance is, not only logical, but also one of the most effective treatment options for EoE. There are three types of dietary approaches: (1) elemental diets with an amino acid-based liquid formula[30]; (2) directed elimination diets based on allergy test results[31]; and (3) non-directed, empirical elimination diets[32]. A recent meta-analysis revealed that elemental diets, non-directed diets, and allergy test-directed diets had efficacy rates of 91%, 72%, and 46%, respectively in adults with EoE[33].

Strict elemental diets have been very effective in inducing remission in 88% to 96% of children[30,32,34] and 72% of adults with EoE[35]. The advantages of an elemental diet include rapid remission, balanced nutrition, and no dietary contamination. The disadvantages of this approach are poor palatability, poor patient adherence, probable enteral feeding tube placement, and cost-prohibitive elemental formulas[36].

Directed elimination diets are based on allergy test results. The most common allergy tests used are radioallergosorbent (RAST), skin prick tests (SPT) and atopy patch test (APT). Elimination diets directed by allergy testing achieved complete clinical and histological remission in 78% of pediatric subjects and only 26% of adult subjects with EoE[31,37]. The prospect of eliminating only 1-2 foods based on allergy tests is appealing and practical to patients. However, allergy testing can be time-consuming, expensive, and limited by false-positives rates. Currently, atopy patch testing is not standardized.

The empiric elimination diet or six food elimination diet (SFED) excludes the most common allergenic foods (milk, wheat, egg, soy, nuts and fish) and successfully improved histology and alleviated symptoms in 74% of pediatric patients with EoE[32]. The process of reintroducing these foods identified milk as the most likely offending agent, followed by wheat, egg and soy in children[38]. SFED demonstrated 70% efficacy in adult patients with EoE, where wheat and milk were the most common offending foods[39]. SFED achieves better efficacy without needing allergy testing while still allowing a variety of foods in the patient's diet. However, SFED entails stepwise reintroduction of foods with multiple follow-up endoscopies, which makes the cumbersome process unappealing. In addition, the diet imposes risk of nutritional deficiencies, and each re-introduction step poses a risk for disease relapse by re-introducing a potential offending food. Overall, while any dietary therapy can be extremely effective in EoE, dietary guidance such as a registered dietician can safeguard from the pitfalls of patient adherence, contamination, and nutritional deficiencies.

Anti-IgE therapy

There might be a relationship between EoE and IgE-

mediated food allergy. Traditionally, IgE-mediated hypersensitivity requires Th2 cells to signal B cell class switching to generate antigen-specific IgE. Cross-linking of allergen antigen, IgE, and Fc receptors on mast cells or basophils activate the release of inflammatory mediators such as histamine, tryptase, and leukotrienes. In EoE patients, the prevalence of IgE-mediated food allergies is about 15%-43%[1]. Food-specific IgE has been detected by skin prick test with more success in children than adults[37,40]. IgE-bearing mast cells and B cells are detected at elevated levels in the esophageal biopsies of EoE patients[41].

Omalizumab is an anti-IgE monoclonal antibody used to control asthma in severely allergic asthmatic patients. Results of an open labeled study, where the majority of the EoE subjects were adolescents, showed significant reduction in esophageal tissue IgE levels. Fifteen subjects were administered omalizumab for 3 mo. Thirty-three percent of the subjects demonstrated complete clinical and histological remission. The responders had low peripheral blood absolute eosinophil counts, suggesting that perhaps in a subset of EoE patients, IgE might play a role in the pathophysiology[42]. However, EoE might not be entirely dependent on IgE-mediated inflammation, since IgE-deficient mice continued to develop esophageal inflammation[43,44]. Furthermore, in a prospective trial, omalizumab was ineffective in reducing symptoms and esophageal eosinophilia in adults with EoE compared to placebo[45,46]. Thus, strategies to stratify and identify potential candidates for anti-IgE therapy have been proposed and will require larger clinical trials.

TARGETING THE ESOPHAGEAL EPITHELIAL BARRIER

In health, the esophagus has a stratified epithelium forming a barrier from luminal contents including food allergens, aeroallergens, bacteria, and gastric acid refluxate. Disturbances in the epithelial barrier might allow allergens to enter the esophageal epithelium initiating or perpetuating an allergic inflammation. Histological findings of spongiosis or dilated intercellular spaces in active EoE implicate some impairment in epithelial barrier[1]. Mucosal integrity, based on intraluminal impedance measurements, was compromised in EoE patients[47]. Measurements of permeability and transepithelial electrical resistance on esophageal tissue biopsies also indicate barrier disturbances[48]. Expression of cell junction and adhesion proteins (E-cadherin, claudin-1, zonula occludens-3, and desmoglein-1)[48-50] and epithelial differentiation genes (involucrin, small proline-rich protein, and filaggrin) were downregulated[51]. Restoring epithelial barrier function might be an appropriate therapeutic target. Treatment with high-dose esomeprazole improved mucosal integrity in PPI-REE patients[52]. Currently, investigators are examining the effect of sucralfate slurry on dilated intercellular spaces, tight junctions, mucosal impedance and mucosal activity in patient with EoE (NCT02353078 www.clinicaltrials.gov). Sucralfate is a medication originally developed to treat mucosal ulceration due to acid-peptic diseases. While the exact mechanism of the drug is unknown, binding to and protection of exposed eroded areas, increased prostaglandin production, improved vascular flow, and increased mucus production are all proposed mechanisms.

TARGETING IMMUNE CELLS (EOSINOPHILS, TH2 LYMPHOCYTES, AND MAST CELLS)

Topical corticosteroids

Corticosteroids have pleiotropic effects on immune cells, esophageal cells, and mediators relevant to EoE pathogenesis. After steroid therapy, eosinophils from EoE patients had decreased surface marker CD18 which might impair eosinophil cell adhesion[53]. The elevated numbers of CD3+, CD4+, and CD8+ T cells in the esophageal mucosa of EoE patients were decreased after steroid treatment[54,55]. Mast cell associated genes were downregulated after steroid therapy in EoE patients[56]. Furthermore, steroid therapy reversed IL-13-induced gene transcriptome[57], attenuated IL-5 gene expression[58], and modulated transforming growth factor (TGF)β1 expression and SMAD 2/3 phosphorylation in the esophagus[59].

It is clear from several recent meta-analyses and systematic reviews of randomized controlled trials that topical steroid therapy significantly reduces esophageal eosinophilia in EoE[60-62]. However, there was no clear trend in symptom response, and this may be due to the lack of validated patient reported outcome measures during those trials[19,21,63-67]. In children, both fluticasone[63] and oral viscous budesonide (OVB)[66] have demonstrated histological remission after 3 mo of intervention in double blind randomized placebo controlled trials which correlated to symptom improvement. Subepithelial fibrosis was seen to improve with OVB therapy. In adults, fluticasone induced histological remission in 62% of adults, however the response was not accompanied by a relief of symptomatic dysphagia[64]. Long-term data on budesonide as a maintenance therapy was assimilated by Straumann *et al*[68]. Patients who took low dose swallowed budesonide for 50 wk achieved partial remission (*i.e.,* reduced eosinophilia) compared to placebo. In addition, mucosal remodeling was attenuated in the treatment group without signs of epithelial atrophy[68]. Overall, the disease typically relapses within 2-9 mo after discontinuation of steroids[34,69,70].

Swallowed fluticasone propionate and oral viscous budesonide have both been commonly used as topical

applications of steroids in EoE. With fluticasone, patients are instructed to puff the inhaler into the mouth. The patients hold their breath, instead of inhaling, and swallow the aerosolized medication directly. With OVB, patients are directed to mix the contents of the budesonide respules (0.5 mg/2 mL) with sucralose to create a slurry; although other various viscous agents such as honey, apple sauce, amino acid-based semisolid, and food thickeners have been used successfully[71]. Currently, the American College of Gastroenterology (ACG) guidelines recommend Fluticasone 880-1760 mcg/d in a divided dose for adults and 88-440 mcg/d for children. The dosage of OVB is 1 mg/d for children and 2 mg/d in divided doses for adults. The recommended duration is 8 wk for topical steroid therapy[13].

Other formulations of topical steroids are currently investigated. A recent randomized controlled trial demonstrated that an effervescent tablet of budesonide was comparable to viscous budesonide in remission rates and the preferred choice by patients[72]. Two more trials will be examining the efficacy and tolerability of effervescent budesonide over placebo (NCT02434029 and NCT02493335, www.clinicaltrials.gov).

Topical steroids are generally well tolerated, with the rare exception of esophageal candidiasis. In addition, topical steroid did not suppress adrenal function in EoE pediatric patients during 8-43 wk of therapy[73]. Nevertheless, ciclesonide, another corticosteroid with lower systemic bioavailability and favorable safety profile, has been proposed and used successfully in a few pediatric cases of EoE[74,75].

Immunomodulators

Systemic steroid, like prednisone, was one of the earliest pharmacologic agents used in EoE[76], however a 40% rate of systemic adverse effects has essentially reserved the drug for only severe refractory cases[70]. Yet, in the event of severe cases, steroid sparing agents such as azathioprine and 6-mercaptopurine have also been proposed. In a case series, 3 EoE patients were treated with azathioprine or 6-mercaptopurine and achieve histological remission[77]. Patients were successfully tapered off of steroids; however, the disease relapsed after the immunomodulators were discontinued. Therefore, this study showed that immunosuppressive therapy was necessary to maintain disease control.

CRTH2 antagonist

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is expressed by Th2 lymphocytes, eosinophils, and basophils[78]. Therefore, CRTH2 is an appealing target for Th2-type inflammatory disorders. CRTH2 antagonists interfere with the prostaglandin pathway, blocking the prostaglandin D2 receptor, subsequently preventing the activation and the recruitment of the CRTH2-expressing inflammatory cells. OC000459, a CRTH2 antagonist, is a promising new drug for the treatment of allergic diseases because it is selective and is orally bioavailable. A randomized controlled trial demonstrated a modest improvement in eosinophilic inflammation and clinical symptoms in 26 severe, steroid-refractory EoE adults compared to placebo[79]. The 8 wk drug therapy was well-tolerated. Further studies are needed to determine if the drug can achieve greater improvement in moderately-active EoE patients.

Mast cell stabilizers

Mast cells release inflammatory mediators (TGFβ1, IL-4, IL-13, leukotrienes, and tryptase), and several human and animal EoE studies suggest that mast cells might contribute independently or in tandem with eosinophils to esophageal inflammation[56,80-84]. The mast cell mediator prostaglandin D2 induces eosinophil trafficking in an EoE guinea pig model[84]. Tryptase and IgE immunostaining confirmed that IgE-bearing mast cells are increased in the esophageal mucosa[85] and smooth muscle layer of EoE patients[81]. The expression of TGFβ1 suggests that mast cells might mediate esophageal contraction and remodeling. Unfortunately, earlier small case series demonstrated unsuccessful results with mast cell stabilizer cromolyn sodium[1,34]. There is a double-blind, randomized controlled study examining the safety and efficacy of cromolyn sodium for the treatment of EoE (NCT02371941 www.clinicaltrials.gov).

TARGETING INFLAMMATORY MEDIATORS

IL-5

IL-5 promotes eosinophil proliferation in the bone marrow and primes eosinophils for cytokine stimulation. EoE murine studies established that eosinophil trafficking is IL-5-dependent[86] and drives esophageal remodeling and fibrosis[87-89]. Reslizumab, a humanized monoclonal antibody to IL-5, neutralizes circulating IL-5 by preventing it from binding to its receptor which is expressed by several cells, including eosinophils. A randomized controlled trial conducted in children and adolescents did not show statistically significant symptomatic improvement with reslizumab compared to placebo, but did show significant improvement in esophageal eosinophilia compared to placebo[90]. Mepolizumab is another monoclonal antibody to IL-5. In a randomized controlled trial with adult EoE patients, intraepithelial eosinophil numbers decreased in esophageal tissues. The expression of molecules associated with esophageal remodeling was reversed. However, there was minimal improvement in the clinical symptoms[91]. In addition, a mepolizumab study in pediatric subjects with EoE demonstrated significantly fewer mast cells, IL-9 cells, and mast cell-eosinophil couplets in responders[92].

IL-13

IL-13 appears to activate the local tissue inflammatory response in Th2-associated diseases. The EoE gene transcriptome analysis discovered many IL-13-inducible genes responsible for pathogenesis[26,57]. Elevated IL-13 mRNA levels are detected in esophageal biopsies from EoE patients[41,57]. IL-13 decreases esophageal epithelial cell differentiation, a process that may be critical for maintaining the barrier function of the esophageal mucosa[51]. Additionally, IL-13 mediates eotaxin-1, eotaxin-2, and eotaxin-3 expression *via* STAT6 in esophageal epithelial cells from mice[93] and humans[51,57,94]. Eotaxin-3 is the highest upregulated gene in the EoE transcriptome[26]. Mice with genetic deletion of the eotaxin-3 receptor were protected from allergen-induced EoE[26]. Animal studies confirmed that IL-13 facilitates eosinophil recruitment[95] and induces features of esophageal remodeling[96]. A randomized controlled trial tested QAX576, a monoclonal antibody against IL-13, with promising results[97]. QAX576 was well-tolerated, although treated subjects did not meet the primary endpoint. Intraepithelial eosinophils were reduced by 60%, and there was some symptom improvement. Most strikingly, genetic markers of EoE inflammation, including eotaxin-3, periostin, mast cells markers, and barrier function, were modified after treatment. This study provides proof-of-principal that the biology of a human Th2-driven disease at the molecular level in a relevant tissue can be altered by a specific anti-IL-13 antibody. Presently, a double-blind, randomized controlled trial will evaluate the efficacy and safety of the anti-IL-13 monoclonal antibody RPC4046 in EoE adults (NCT02098473 www.clinicaltrials.gov).

IL-4

IL-4 expression is higher in EoE patients compare to control cases[25,98]. While IL-4 and IL-13 often share similar downstream effects, such as driving eotaxin-3 expression in esophageal epithelial cells, the role of IL-4 has not been clearly delineated in EoE[94,99]. In other allergic disorders, IL-4 induces naïve T cells to differentiate to Th2 cells. IL-4 also facilitates B cell class switching to IgE. Dupilumab, a human monoclonal antibody that blocks the IL-4 receptor α subunit, is therapeutically effective in patients with asthma and elevated eosinophil levels[100]. The blockade Th2-mediated inflammation by dupilumab was also seen in atopic dermatitis[101]. Currently, a randomized controlled trial is underway to study dupilumab in adults with active EoE. The study will assess the clinical efficacy of repeat subcutaneous doses of dupilumab to relieve symptoms in adult patients with active, moderate to severe EoE (NCT02379052 www.clinicaltrials.gov).

TGFβ1

Fibrogenesis is part of normal repair response to epithelial injury, in which fibroblasts synthesize extracellular matrix proteins such as collagen, fibronectin, and tenascin-C for wound healing[28]. A chronic inflammatory disorder such as EoE will progress to fibrostenotic complications[2,3], such as food impactions, fibrotic strictures, esophageal narrowing, mucosal tears, and transmural perforations[1,8,102]. TGFβ1 is a well-known fibrogenic factor in many fibrotic diseases. It is produced by eosinophils, mast cells, and other inflammatory cells, and is directly involved in esophageal fibrous remodeling in both pediatric and adult patients[103,104]. Mast cells infiltrating the esophageal smooth muscle layer of EoE patients express TGFβ1[81]. Silencing TGFβ1 molecular targets such as phospholamban[105] and Smad3[106] can diminish smooth muscle cell contraction and abrogated fibrosis and angiogenesis in mice. Angiotensin Ⅱ receptor blockers inhibit TGFβ, and have been studied in connective tissue diseases such as Marfan's syndrome where there is excessive TGFβ production[107]. An open-label trial of losartan, an angiotensin Ⅱ receptor blocker, in EoE subjects with or without a connective tissue disorder is underway. The trial will measure histologic improvement, symptomatic improvement, reduction in TGFβ, and drug safety (NCT01808196 www.clinicaltrials.gov).

Tumor necrosis factor

Tumor necrosis factor (TNF)α is a prominent inflammatory mediator in many chronic inflammatory diseases, such as Crohns disease. Not surprisingly, TNFα is found to be upregulated and highly expressed by esophageal epithelial cells in patients with EoE[24,57]. Evidence of TNFα signaling, including NFκB subunits p50 and p65, are detected in EoE and might play a role in angiogensis[108]. Infliximab, a chimeric IgG1 monoclonal antibody, is a potent inhibitor of TNFα. Thus far, a case series of 3 adults with corticosteroid-dependent EoE demonstrated variable histological and symptom response with two 5 mg/kg doses given every two weeks[109]. Although infliximab was well-tolerated in these cases, further studies are warranted to establish efficacy.

Leukotriene

Leukotrienes, in particular, cysteinyl-leukotrienes (LTC_4, LTD_4, and LTE_4) are potent lipid mediators synthesized from arachidonic acid *via* the 5-lipoxygenase pathway in immune cells. Cysteinyl-leukotrienes are best known for their pathophysiologic role in asthma, and many of their effects are mediated through their receptor $CysLT_1$ which are expressed on eosinophils, basophils, mast cells, T cells, airway smooth muscle cells, bronchial fibroblasts, and vascular endothelial cells. Montelukast is a $CysLT_1$ receptor antagonist that is effective in asthma treatment. Similarities in pathophysiology between asthma and EoE prompted trials of montelukast in EoE. In a case series of 8 pediatric EoE patients, 6 had symptomatic relief with

montelukast[110]. Similarly, another 3 out of 8 pediatric EoE patients reported symptomatic response, but histological response to montelukast could not be verified[111]. In a prospective study, montelukast failed to maintain steroid-induced remission in 11 adult EoE subjects[112]. Currently, there is a randomized controlled study evaluating clinical effectiveness of montelukast compared to placebo on prevention of dysphagia and food impaction in EoE subjects (NCT00511316, www.clinicaltrials.gov). The study will also examine tolerability and safety of the drug. Another study will compare response to treatment of EoE with montelukast compared to topical fluticasone therapy (NCT01702701, www.clinicaltrials.gov).

PPI THERAPY FOR EOE

As mentioned above, PPI-REE patients might be a subset of EoE patients. There are multiple conceivable mechanisms whereby EoE patients might benefit from PPI-induced acid suppression[15]. Reducing acid exposure might ameliorate inflammatory cytokines and pain related to acid-induced injury. In addition, acid reflux might exacerbate esophageal epithelial permeability facilitating allergen entry in EoE. Indeed, mucosal integrity, determined by electrical tissue impedance and transepithelial electrical resistance, was impaired in both EoE and PPI-REE patients[52]. High-dose PPI therapy improved mucosal integrity in the PPI-REE patients.

EoE patients might benefit from PPIs through mechanisms that are not related to acid suppression. PPIs can inhibit Th2 cytokine-induced eotaxin-3 secretion in esophageal epithelial cell, thereby potentially reducing eosinophil recruitment[94,99]. Eotaxin-3 expression by epithelial cells in the esophageal biopsies of children with esophageal eosinophilia was examined before and after PPI therapy[113]. With PPI therapy, subjects achieved a decrease in eotaxin-3 expression in the proximal esophagus, where gastroesophageal reflux is unlikely to reach, suggesting that anti-inflammatory effects might be the predominant therapeutic effect[113]. Other anti-inflammatory effects of PPIs include inhibition of immune cell functions, anti-oxidant properties, minimizing cell adhesion molecules, and decreasing inflammatory cytokines[15]. Finally, EoE transcriptome expression (an array of genes associated with eosinophilia, mastocytosis, tissue remodeling, and impaired barrier function) reversed in PPI-REE patients after PPI therapy substantiating that PPIs have therapeutic properties that target an allergic inflammation[23].

Overall, PPIs have multiple effects that might benefit EoE patients. The diagnosis of EoE should be based on the conceptual definition that the patient has an "immune/antigen-mediated" disease. Thus, for any patient who has esophageal symptoms and esophageal eosinophilia, a clinical and/or histological response to PPIs does not necessarily implicate GERD as the sole diagnosis and does not rule out EoE. Using a trial of PPI therapy as a diagnostic screen should be done with a caveat in mind. Instead, high-dose PPI therapy should be considered as a therapeutic option rather than a diagnostic screen for EoE.

DILATION

As previously mentioned, medical therapies can attenuate esophageal inflammation, ideally preventing further fibrosis and remodeling. The ability for any of these therapies to reverse long-term fibrosis and remodeling still remains to be substantiated. Although medical therapy is a logical first approach, clinicians might have to resort to dilating high-grade fibrostenotic lesions to provide symptomatic relief[114]. High complication rates with esophageal dilation procedures in EoE patients were initial concerns, but a recent meta-analysis reports complication (perforation, haemorrhage and chest pain requiring hospitalization) rate of < 1% at medical centers experienced with the EoE population[115]. Although dilation does not address histological inflammation[116], the procedure is 75% effective in improving short term clinical symptoms[115]. However, without medical therapy to abate the inflammation, EoE patients will require repeat dilation procedures as fibrostenotic lesions recur. Recently, a randomized blinded controlled trial evaluated response to dilation as an early treatment strategy in adults with dysphagia (without severe strictures) and esophageal eosinophilia[114]. However, the subjects treated with medications (PPI and fluticasone) and randomized to dilation procedures did not have any better dysphagia score outcomes compared to subjects treated with medical therapy alone. Thus, dilation should probably be considered an adjuvant therapy to a long-standing medical therapy.

CONCLUSION

EoE is a chronic inflammatory disease that can lead to fibrosis and remodeling and requires long-term treatment. EoE treatment goals include symptom resolution, induction and maintenance of disease remission, prevention of fibrostenotic complication, maintenance of quality of life, and minimizing adverse effect from medical therapies. Current and emerging medical therapies are designed to interrupt the inflammatory cascade in EoE. Esophageal dilation disrupts fibrotic strictures, providing symptomatic relief, but does not address the underlying inflammatory process. Distinguishing GERD and EoE remains a challenge. However, a response to PPI therapy does not provide diagnostic utility since EoE patients may benefit from both acid-suppressive and anti-inflammatory effects of PPIs. Therefore, PPIs should be considered as a potential therapeutic agent for EoE rather than a diagnostic screen. Much of EoE pathophysiology and natural progression still needs to

be explored to identify novel targets for therapy.

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