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Eosinophilic Esophagitis

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1. Introduction

Eosinophilic gastrointestinal diseases (EGIDS) are immune mediated diseases with varying clinical presentations but are characterized pathologically by eosinophilic infiltrate of the epithelium of the gastrointestinal tract. Eosinophilic esophagitis has become the most recognized entity over the last twenty years and great strides have been made to understand it. In the 1970s and 1980s, case reports of patients with esophageal eosinophilia were reported but the significance of these findings was not known or were attributed to GERD. In the 1990s the field of Pediatric Gastroenterology was emerging and endoscopy of children became more common. In addition, pediatric gastroenterologists knew that inflammation could occur despite macroscopically “normal” appearing tissue and therefore routine biopsies during endoscopy have been standard of care. This led to wider understanding of the clinical presentation and outcomes of children with prominent eosinophilia of the esophagus. These children did not respond to the typical antacid regimen. They had a wide range of clinical symptoms including vomiting, regurgitation, and abdominal pain and feeding refusal. It was also noted that many had concurrent atopic diseases including food allergies, eczema and asthma.[1-4] The fields of allergy and gastroenterology were beginning to converge on a disease process that would prove more complex to manage than many other food allergies. Today gastroenterologists and allergists have come to depend on one other in the management of these patients.

Eosinophilic esophagitis is becoming a recognized common cause of esophagitis in children and adults. The most current definition comes from the consensus statement published in 2011 in The Journal of Allergy and Clinical Immunology. The new criteria is less restrictive than definitions put forth in the past. In addition, the authors changed the abbreviation from EE to EoE because across disciplines EE can have different meanings (e.g. erosive esophagitis). This expert panel wanted to conceptualize the definition so that it could represent the wide range of patients and clinical scenarios. The expert panel agreed upon the definition that “eosino-

philic esophagitis represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation".[5]

Histologic criteria include the presence of ≥ 15 eosinophils per high power field on esophageal biopsy. This requirement should make diagnosis more standardized; however, the definition of "high power" field can vary and therefore change the number of eosinophils reported. They did allow for exceptions to the 15 per high power field in the case of other histologic features including microabscess, superficial layering or extracellular eosinophilic granules. [5]

2. Epidemiology

The epidemiology of eosinophilic esophagitis is becoming better understood. From multiple studies it has become apparent that EoE affects males at least 3 times more frequently than females.[6-11] EoE patients are more likely to have atopic disease than the general population. [12-17] Whites appear to have a higher incidence than other races. All age groups are affected including infants and there is a report of a 98 year old with EoE.[11] However, most patients are children, adolescents and adults younger than 50 years old. In a large epidemiological study the prevalence was highest in men age 35-39 years old.[18]

The prevalence and incidence has been hard to determine. Data suggests that the incidence and prevalence is increasing. While it could be hypothesized that this was due to increased awareness, retrospective studies of esophageal biopsy specimens have indicated that the incidence and prevalence are truly increasing. This increase in incidence and prevalence remains when adjusted for the increased use of endoscopy.[19, 20] The incidence has been reported to be 6 to 13 cases per 100,000 in studies from the United States, Canada, and Switzerland.[13, 21-23] Denmark and Netherlands report lower incidence at less than 2 cases per 100,000.[24] The prevalence has been estimated anywhere between 10-80 cases per 100,000, depending on the population being studied.[18] A recent study using a large US database of health insurance claims of over 35 million patients showed a period prevalence of 56.7 per 100,000 through the years 2009-2011.[18]

3. Differential diagnosis

The differential diagnosis for esophageal eosinophilia includes celiac disease, Crohn's disease, esophageal achalasia, connective tissue disorders, drug reactions, hypereosinophilic syndromes and graft versus host disease and these disorders need to be ruled out prior to making the diagnosis of EoE. The most problematic differential diagnosis is gastroesophageal reflux (GERD). In the past, eosinophilia was attributed to GERD. During the treatment of patients with prominent eosinophilic infiltrate it was noted that they were less responsive to antacids, both clinically and histologically. Trying to understand the relationship between GERD, eosinophilia of the esophagus and EoE is one of the most important and difficult tasks facing

clinicians who diagnose and treat EoE. Food allergy is also a major component of EoE and dietary therapy can be first line therapy in many cases. The relationship between food allergy and EoE is also only partially realized.

4. Eosinophils

An understanding of EoE requires a review of the primary effector cell in the pathology, the eosinophil. New developments in our understanding of eosinophil responses reveal that their role in immunology goes beyond attacking helminthes. Eosinophils are highly complex hematopoietic cells which participate actively in the immune response. First, eosinophil released granule products such as eosinophil cationic protein (ECP) are capable of chemoattracting antigen presenting cells such as macrophages.[25] This granule is believed to have direct antimicrobial action as well as directing macrophage recruitment to the site of ECP release. Recruitment of myeloid dendritic cells to draining lymph nodes, a critical step to specific immune responses, is influenced by eosinophils.[26] Further downstream, in the immunologic response, eosinophils are capable of regulating B cell numbers via influencing B cell proliferation.[27] Further evidence that eosinophils can participate in the immune response to pathogens is the presence of pattern recognition receptors on the eosinophil receptor. These toll-like receptors, NOD, dectin-1 and RAGE receptors are innate, non-specific responses to various elements of the microbial cell wall which result in initiating and amplifying the host immune response.[28] Studies have demonstrated toll-like receptor expression on eosinophils occurs in EoE.[29] The immunobiology of the eosinophil is intimately related to the allergic response. The understanding that eosinophils and allergies are related in the experimental research in EoE is new. Due to the recent gains in the knowledge of the pathophysiology of EoE there are gaps in the clinical applications. Therefore other atopic diseases, such as asthma, will be utilized as a model to demonstrate the eosinophil's complex capabilities. Particular emphasis will be placed on those components of the allergic response which likely contribute to EoE.

Eosinophils are hematopoietic cells, derived from the bone marrow. Normal hematopoiesis involves tight control on eosinophil differentiation from a common progenitor cell. New data suggests that eosinophils and basophils share a common lineage with the erythrocytes and megakaryocytes.[30] However, commitment from the common progenitor cell into an eosinophil progenitor (CD 34+IL5R+) requires the presence of IL-5 predominately, but GM-CSF and IL-3 also affect eosinophilopoiesis.[31] Sources of IL-5 in the bone marrow include the bone marrow stromal cell, hematopoietic cells, T lymphocytes and bone marrow endothelial cells.[32] Data suggests that a newly discovered hematopoietic cell ILC2, an innate lymphoid cell present locally in peripheral tissues, may be capable of controlling eosinophilopoiesis. [33] These ILC2 cells produce profound amounts of IL-5 which is released into the systemic circulation directing the bone marrow to increase eosinophil production. IL-5's role in EoE is under investigation, as it has been found in the blood vessels of esophageal biopsies of pediatric EoE patients.[34]

Increases of eosinophil progenitor cells and mature eosinophils in the bone marrow are described in both human and murine studies of allergen sensitization and occurs independent of T lymphocytes or specific IgE activation of the bone marrow.[35-37] This model of accelerated response of eosinophilopoiesis is linked to an acute response to allergens in multiple strains of mice. However, the eosinophilic potential to have ongoing bone marrow eosinophilia linked to chronic disease and fibrosis development in the asthmatic airway may not be a universal response in the disease and may require a specific genetic background. [38] This may have implications for disease severity in both asthma and EoE in determining which individuals have disease progression due to eosinophil influenced severe fibrosis.

Eosinophil progenitor cells may be able to finish differentiation to mature eosinophils locally in the effected peripheral tissue, like the esophagus, stomach and intestines. Eosinophil progenitors are released into the peripheral blood stream in asthmatic individuals and are attracted to peripheral tissues that are involved in the asthmatic response.[39] Interestingly, topical glucocorticoid therapy in asthma decreases eosinophil progenitors circulating in the peripheral blood. [37] In addition, interfering with chemotactic signaling of eosinophil progenitors early in the asthmatic response to allergen challenge to the lung decreases lung eosinophil progenitor and mature eosinophil numbers.[39] This demonstrates that control of eosinophilopoiesis may be an important component to controlling eosinophil derived diseases. Investigations into the potential for eosinophilic mucosa to support eosinophilopoiesis could provide a key understanding of the pathophysiology of EoE.

Progenitor cells are attracted to peripheral tissue and so are mature eosinophils. The primary chemokines responsible for recruiting mature eosinophils to their targets are IL-5, eotaxin, MCP and RANTES.[40] These cytokines are produced by inflammatory cells present in the tissue during allergic responses. Other cytokines released by tissue cells in the allergic response such as IL-4 and IL-13 may play an indirect role in eosinophil trafficking role by increasing eotaxin expression. Epithelial cell production of IL-5, IL-13 and eotaxin has been found in biopsies obtained from pediatric EoE patient.[34, 41] and are decreased with glucocorticoid therapy in EoE. Blockade of these chemotactic signals results in reduction of the eosinophilic response peripherally.

Once recruited to peripheral tissues, eosinophils are activated by multiple extracellular proteins and cytokines. Eosinophils have integrins on their surface that interact with the extracellular matrix. This interaction can increase survival of eosinophils and also increase recruitment of more eosinophils through several pathways. For instance, platelet-activating factor primes eosinophil adherence to tissue through both beta-1 and beta-2 integrins.[40] Periostin, an extracellular matrix protein, is a strong chemotactic agent.[42] Periostin production has been shown to be inducible by transforming growth factor-beta and IL-13 after allergen exposure in a corresponding murine model of EoE.[43] Periostin exists in both the human lung and esophagus. Levels of periostin have been found to be higher in EoE patients than controls. Increased accumulation of eosinophils was correlated to increased levels of periostin in these studies.[44] Therefore it may be that periostin recruits and retains eosinophils at the peripheral tissue in eosinophilic disease. Fibronectin is another extracellular matrix protein that binds

with Beta-1 integrin (VL-4) on the surface of eosinophils. This interaction has shown to enhance eosinophil survival.[45]

Therapeutic approaches that target the adhesion and interactions of eosinophils with tissue and plasma elements will be difficult due to multiple interactions and pathways involved once eosinophils are activated. Highly activated integrin molecules on eosinophils are associated with survival independent of exogenous IL-5 signaling.[42, 46] Eosinophils activated by endothelial fibronectin will also autologously produce survival factors including IL-5, IL-3 and GM-CSF.[47] Dexamethasone reduces the endothelial production of these survival factors.[48] However, this autologous production of survival factors from adherent stimulated eosinophils will make development of a novel single agent anti-cytokine therapy to treat EoE more difficult. The capability of the eosinophil to survive without exogenous IL-5 will also limit the use of anti-IL-5 therapies as sole pharmacotherapy in the armamentarium of EoE treatment.

Negative regulators of chemotaxis and survival of eosinophils include, IL-12 which reduces platelet activating effects on eosinophils and reduces eotaxin dependent tissue migration.[49] Activation of the Siglec-F receptor on eosinophils induces eosinophil apoptosis. IL-5 and GM-CSF failed to rescue eosinophils from this fate, suggesting that this may be one viable way to eliminate eosinophils once they have migrated to peripheral tissues.[50] A proof of concept study has been performed in a murine model of allergic EoE in which Siglec-F activation resulted in decreased eosinophil numbers in the esophagus.[51] Other inhibitory mechanisms which the immune system uses, such as FOXP3, CD25+and TH17 may play a role in this process.[52] While TGF-beta has been linked to fibrotic activity it also has an apoptotic effect on eosinophils as a negative feedback regulatory mechanism.[50-52] The only currently used therapeutic agent which prevents eosinophil priming in eosinophilia is glucocorticoids.[53] Glucocorticoid effect is thought to be from altering eosinophil and other immune mediated cell cytokine production. Glucocorticoids also bias hematopoiesis towards neutrophil production.

5. IgE mediated allergic mechanisms

Allergy is the immune pathway mediated by IgE binding to allergen and subsequently activating mast cell release of prototypic cytokines. These preformed mediators include histamine, tryptase, IL-5, cysteinyl leukotrienes amongst other cytokines. This is known as the immediate phase reaction. It is responsible for the wheal and flare during functional skin prick testing to allergens, and immediate airway contraction in asthma. These agents also cause vomiting, diarrhea, and abdominal cramping after an IgE mediated food allergy. Release of these agents subsequently causes an inflammatory recruitment of eosinophils and lymphocytes, known as the late phase reaction.

Some EoE patients appear to have this basic immediate phase response. IL-5 and IL-13 correlate with eotxin-3 and eosinophil levels.[44] In addition some EoE patients have both eosinophils

and mast cells in esophageal biopsies.[54] In fact, the presence of IgE bearing intraepithelial mast cells in EoE patients distinguished allergic EoE patients from non-allergic EoE patients. [17] Mastocytosis and degranulated mast cells have been found in the biopsies of EoE patient. [55] In asthma, contact of eosinophils with mast cells was the most potent driver of eosinophil survival.[56] The presence of IL-13 in EoE would also increase IL-4 and IL-13 and cause B cell isotype switching to IgE production.

In addition, TH2 cell production of cytokines such as IL-4, 5, 13 is a hallmark feature of allergy. The importance of IL-13 in immediate phase reactions is demonstrated by inhibition of IL-13 by an anti-IL-13 Fab fragment resulting in decreased eosinophilia, inflammatory infiltrate and airway hyper-reactivity in a murine model of asthma.[57] Anti-IL5 therapy is being investigated in eosinophilic diseases such as asthma and Churg Strauss disease. Anti-IL4 therapeutic targets are being investigated in atopic dermatitis. These Th2 driven processes are also amplified by innate lymphoid cells (ILC2) at the mucosal surface. [58] These cytokines along with TGF-beta encourages eosinophil induced fibrosis and motility disorders in EoE patients.[43]

Some allergens will also actively participate in the subsequent immediate phase reactions. Allergens which are proteases (insect derived or fungal) have been found to deceitfully act in an innate fashion with initial exposure. These allergic proteases activate IL-25, IL-33 and TSLP mucosal production resulting in ILC2 activation in the lung tissue.[59] In this study ILC2 expressed IL-5 and IL-13. Eosinophil recruitment has been identified in the lung with fungal chitinase exposure.[60] Interestingly a murine model of EoE induced by cockroach and dust mite has been described.[61] This model was characterized by esophageal eosinophilia, mastocytosis, increased IgE, IL-5 and eotaxin after cockroach and dust mite exposure but not cat or dog exposure. Protease inhibition in a murine asthma model with cockroach extract reduced eosinophil counts in BALF.[62]

6. GERD and eosinophils

In 1982 Winter, et al. described esophageal eosinophils in series of pediatric patients and concluded that increased eosinophils was a marker for more severe GERD.[63] Four theories have been proposed for the association between esophageal eosinophilia and GERD. First, EoE and GERD can both be present but they are unrelated. The 2011 consensus statement has chosen not to exclude the diagnosis of EoE even in the setting of abnormal pH probe. This recognizes the hypothesis that GERD and EoE can coexist. The basis of this hypothesis from an epidemiologic view, is that approximately 20% of adults have GERD so a certain percentage of adult EoE patients will also have GERD. [64, 65] In addition, pathologic GERD is rare in children with EoE.[66] This latter claim could be disputed since pH monitoring is not always done in children and there are no standardized norms. However, other research has found higher incidences of GERD among adult patients with EoE.[67, 68]

Another proposed mechanism is that GERD causes esophageal eosinophilia but it is not eosinophilic esophagitis. The criteria for the number of esophageal eosinophils to be greater

than 20 was suggested after it was noted that patients with more than 15 eos/hpf were less likely to respond to anti-reflux medication.[69, 70] In lab models it has been shown that acid stimulates the release of many substances that could potentially attract and activate eosinophils. These substances include platelet activating factor, interleukin-8, eotaxin-1, eotaxin-2, exotoxin-3, macrophage inflammatory protein and RANTES (regulated upon activation of normal T cell expressed and secreted).[71-76] These factors have also been isolated from biopsy specimens from patients with GERD.[76] However, it is still not known if the eosinophilia associated with GERD is a separate entity from eosinophilic esophagitis.

Another hypothesis is that EoE contributes to or causes GERD. Eosinophils produce substances that are cytotoxic and other factors that may alter esophageal motility. For example, eosinophils produce vasoactive intestinal peptide and PAF which can lower esophageal pressure, inducing GERD.[77, 78] Secretion of IL-6 can weaken esophageal muscle contraction and peristalsis.[79] In asthma, cytotoxic substances can damage tight junctions.[80] In the esophagus this could lead to increased permeability to acid and induce pain receptors and the clinical symptoms of GERD.[81, 82]

Finally, one hypothesis blames GERD for EoE. GERD can cause inflammation and increase the permeability of the esophageal epithelium; thereby allowing large molecules to enter. This influx of gastric contents could include potential allergens that induce EoE.[72, 74, 83-85] In addition, refluxed gastric contents can activate many eosinophil chemoattractants including IL-8, PAF, eotaxin-1-3 and MIP-1 α . [74, 85] Other non-eosinophil immune cells and inflammatory mediators can also be attracted to the esophagus after exposure to gastric material.[86] Proving any of these is a complex task involving multiple pathways in the systemic and gastrointestinal immune systems.

7. Proton pump inhibitors

Due to the complexity of the relationship between GERD and EoE, proton pump inhibitors have been at the center of much therapeutic research. When esophageal eosinophils were first described they were attributed to GERD. Therefore patients were treated with anti-acid medications. As mentioned earlier, only some of these patients responded to this therapy. These patients are now considered to have “proton pump inhibitor responsive eosinophilic esophagitis” (PPI-REE) according to the 2011 consensus recommendations.[5] The consensus statement does not recommend PPI as a sole treatment for patients with esophageal eosinophils that are not responsive to PPI therapy. However, they state that even these patients could be treated with a PPI in addition to other treatment for their EoE. The use of PPI in patients with EoE is multifactorial. First, GERD may be a comorbid disease in these patients. These patients may have additional symptomatic relief with PPI therapy. PPI are used in acid suppression because of their inhibitory effect on the H⁺K⁺ATPase of the gastric parietal proton pump cell.[87] According to some hypotheses the suppression of acid in the gastric reflux contents could decrease the production of acid stimulated eosinophilic chemoattractants and other inflammatory cytokines. Also, decreasing esophageal acid damage would decrease

esophageal permeability and exposure to allergens which can induce eosinophilia. However, PPI's may affect esophageal eosinophilia through other mechanisms outside of acid suppression. They have been found to have anti-inflammatory effects on epithelial and endothelial cells. They have demonstrated inhibitory effects against eotaxin-3 production and decrease the expression of adhesion molecules and other inflammatory cytokines.[88, 89] PPI's also display anti-oxidant properties, including scavenging hydroxyl radicals, preventing oxidative damage, and increasing levels of other anti-oxidants.[90-94] Proton pumps are found on cell types other than parietal cells including neutrophils and monocytes. In vitro studies have demonstrated PPI's inhibit the oxidative burst, impair phagocytosis, impair neutrophil migration, and decrease expression of adhesion molecules on monocytes and neutrophils.[95-98] Despite these added effects of PPI's, they cannot be used alone to treat EoE.[5]

8. Food allergy and dietary therapy

The link between allergens and EoE has now been accepted; however, the best way to determine which allergens are most responsible and in which patients is still an area undergoing intense research. Food elimination was first described by Kelly, et al. in 1995 with positive results.[99] Currently there are three frequently prescribed dietary therapies. First, complete elimination diet using amino acid-based formula. Second, six food elimination diet (SFED), which restricts milk, soy, eggs, wheat, tree nuts/peanuts, and fish/shellfish. Last, targeted elimination diet (TED) based off of skin prick and atopy patch testing. This last therapy sometimes includes combination of empiric six food elimination and targeted food elimination.

In a study of EoE patients by Spergel, et al. they determined food allergen prevalence through biopsy results and symptom reports. They found the most common food allergen, diagnosed by both symptoms and biopsy findings, in these patients was milk. Most common food allergens diagnosed with biopsy were milk, egg, wheat, followed by beef, soy and chicken. The most common foods diagnosed by symptoms were milk, egg and soy.[3] This has been substantiated in the EoE literature where many of the studies have also used skin prick testing and atopy patch testing to determine contributing food allergens.[9, 10, 100-103] The most common food allergies reported in the EoE literature are milk, eggs, soy, wheat, nuts (peanuts and tree nuts), and fish/shellfish.[100, 104, 105]

Henderson et al., in a retrospective study compared complete food elimination, targeted elimination diet based from skin prick and atopy testing and six food elimination diet to determine the effectiveness of each therapy.[6] They identified ninety eight patients that were proton pump resistant and non-steroid treated who went on dietary therapy. They rated remission as complete (<1 eos/hpf), partial (1-15 eos/hpf) and non-remission (>15 eos/hpf). Patients on complete elimination diet had significantly higher complete remission rate (<1 eos/hpf) and lower non-remission rate than the targeted elimination diet. They concluded that the complete elimination diet was superior to targeted elimination or the six food elimination diet and there was no difference between SFED and TED.[6] Other studies have shown similar

results with a histologic remission rate for complete elimination diet to be over 90%.[106] Studies of SFED in adults and children have shown that majority of patients have complete histologic response with rates varying from 64-85%. A greater proportion have significant response even if it is not complete resolution.[102, 105, 107]

Gonsalves' study of adults with EoE all patients had skin prick testing for aeroallergens and food allergens.[107] In all patients food allergens tested included the food items in the SFED; eggs, milk, peanuts, tree nuts, fish, shellfish, wheat, and soy, in addition to other foods self-reported as exacerbating symptoms. They found the skin prick test was predictive of only 13% of inciting agents. Also, 67% of the patients who had positive biopsy findings after reintroduction of one of the foods in the SFED had tested negative for that food on SPT. In addition, a recent meta-analysis found that allergy test result-directed food elimination remission rate (<15 eos/hpf) was only 45.5%, with high variability of remission rate between studies.[108, 109] The finding that elemental diet is superior to targeted elimination diet indicates that other pathways are involved.

Aeroallergens/ pollen have also been studied as contributors of eosinophilic esophagitis. Determining if aeroallergens are directly responsible for EoE via ingestion/inhalation or their potential to cross react with sensitized foods is under research. Interestingly, common immune epitopes (pan-allergens) exist between fruits, vegetables and pollen, and shellfish and insects such as cockroach and dust mite. Some of the broad based allergy response may be linked such as ragweed and melon or profiling in birch with celery and apple. In a mouse model, eosinophilic esophagitis could be induced by intranasal aeroallergen exposure.[110] In addition, in both children and adults there is higher incidence of EoE diagnosis in seasons with high aeroallergen counts.[111-113] Some have proposed that esophageal accumulation of eosinophilia in the background of aeroallergens is eotaxin and IL-5 dependent and others propose it is through the TH2/IL-13 response.[114-116] Rayapudi, et al. tested the aeroallergen trigger hypothesis via intranasal cockroach and dust mite allergen exposure on IL-5 and eotaxin levels in CCR-3 deficient mice and wild-type mice. The deficient mice had a dampened esophageal response to the allergens and they concluded indoor insect allergens induce IL-5 and eotaxin mediated EoE.[61] In addition, it has been reported that patients with allergies treated with sublingual pollen immunotherapy may have the unintended side effect of inducing EoE. A recent meta-analysis concluded that 2.7% of patients undergoing oral immune therapy for IgE mediated allergies develop EoE.[117]

Children and adults placed on an elemental diet show resolution of EoE in nearly all patients. Elemental diet may be effective as they could also eliminate pollen pan-allergens and food cross reactivity Issues. Elemental diets may also have effects unrelated to hypersensitivity reactions. This has been investigated by Erwin,et al.[7] Patients with EoE were tested for IgE sensitization using skin prick testing and a screening panel of specific IgE tests. They also tested patients for non-IgE mediated food sensitivities with atopy patch testing. In order to determine overall sensitization they included aeroallergens, common food allergens, cross-reactive carbohydrate determinants, and common commensal elements of the GI tract (*Candida albicans* and *Helicobacter pylori*) in the serum, skin prick testing and atopy patch testing. They found that 20-30% of patients with EoE had no detectable immune sensitivity.[7] This suggests

an intrinsic defect not relatable to allergic immune responses may be responsible. In some patients non-IgE mediated responses are found in asthma, hay fever, and atopic dermatitis at approximately 30% of each patient population. Investigators in these three diseases hypothesize that it is possible to induce pure IL-5 response to stimuli without activating allergic antibody (IgE) responses via IL-4 and IL-13.

9. Steroids

Although corticosteroids are not currently approved for use in EoE, they are frequently used off-label in the treatment of PPI non-responsive esophageal eosinophilia. Dietary management has shown to be effective however, due to compliance difficulties, topical steroids have been used and have been found to be effective in majority of cases of EoE. The two most commonly used preparations are swallowed aerosolized fluticasone propionate and oral viscous budesonide. Systemic corticosteroids can be used if topical steroids are not effective or the patient needs rapid improvement in symptoms, like a food impaction. [118]

Four open-label trials have been conducted using fluticasone propionate.[68, 118-120] Two trials were pediatric patients and two were in adult patients. All four studies reported a significant symptom response rate. Complete symptom response ranged from 90-100% in patients. In addition, all patients on fluticasone had significant decreases in the number of esophageal eosinophils. Complete histologic response rates varied from 21-74% between the studies.[68, 120]

In pediatric and adult placebo controlled trials using fluticasone or oral viscous budesonide, patients on topical steroids had significant histologic response compared to placebo.[121-125] Symptom response was variable in the studies. One study found no significant difference in symptom response between the treatment and placebo groups. However, majority of the patients in the topical steroid group had decrease in dysphagia symptoms, as opposed to less than half in the placebo group.[121]

Four controlled trials have compared a proton pump inhibitor to topical steroids in the adult population. Peterson, et al. compared fluticasone 440 µg twice daily to omeprazole 40 mg once daily for 8 weeks. The histologic response between the two groups was not statistically significant.[67] They also found no difference in dysphagia scores. Moaward, et al studied the same drugs and doses.[126] They also had no statistical difference in histologic response between the two groups at eight weeks. They did have a statistically significant difference in dysphagia scores. The proton pump inhibitor had greater symptom response. The patients with abnormal pH probes were stratified to both groups and these patients had response to omeprazole but not to fluticasone.

Francis, et al. in a prospective trial, compared patients with esophageal eosinophilia who had positive pH probe results compared to patients with negative pH probe results.[127] The positive pH probe patients were prescribed omeprazole 40 mg twice daily and the patients with negative pH probe results were treated with oral viscous budesonide 1 mg twice daily.

The symptom and histologic response rates between the omeprazole and steroid groups was not statistically significant.

Dellon, et al. compared two topical steroid treatments; oral viscous budesonide 1 mg twice daily to nebulized then swallowed budesonide 1 mg twice daily in a randomized trial.[128] They performed scintigraphy to measure esophageal mucosal contact time with the drug. The oral viscous budesonide had statistically significant more mucosal contact time than the nebulized then swallowed budesonide. This correlated with a significant decrease in eosinophil counts in the oral viscous budesonide group. Both groups showed improvement in symptoms and symptom response was not correlated with histologic response.

One randomized, comparator controlled study has been done in pediatrics. This study compared prednisone 1 mg/kg/day (40 mg maximum) to fluticasone propionate 220 µg QID or 440 µg QID (depending on weight) for 4 weeks.[129] The study also had an 8 week weaning protocol. Decrease in esophageal eosinophil counts at 4 weeks were significant in both groups but the prednisone group had a greater degree of histologic response. Those in the prednisone group had 100% symptom resolution at 4 weeks and 97% of fluticasone patients had symptom resolution. Symptom relapse occurred at 12 weeks in approximately 50% of patients, regardless of the treatment received. In addition, systemic adverse effects were reported in 40% of the prednisone group; while the only adverse effect in the fluticasone group was esophageal *Candida* occurrence in 15% of the patients. The incidence of esophageal candidiasis as a result of topical steroid treatment for EoE has been reported in studies of adults and pediatrics at rates ranging from 5-26%. Most report that the infection was found incidentally on endoscopy, was not symptomatic and was the only adverse effect.[68, 120, 121, 123, 125, 126, 128]

Topical steroids have been shown to be effective at inducing histologic and symptom response. However, length of therapy and role of maintenance therapy is still debated. Eosinophilic esophagitis over time, can create fibrosis and subsequent strictures of the esophagus. Whether or not this should be avoided even in asymptomatic patients is the basis of the maintenance therapy debate. Straumann, et al. conducted a placebo controlled maintenance trial comparing those with continued medication therapy versus placebo after steroid induced remission.[122] They reported symptomatic recurrence rate of 64% and histologic relapse of 100% at 1 year in the placebo group. However, others have found that more than half of patients were symptom free after 3-11 years even if they had persistent esophageal eosinophilia.[130, 131] It is not known which patients will develop fibrosis or if long-term topical steroid treatment will prevent it.

The path of eosinophilic esophagitis to fibrosis is being investigated to help distinguish which patients should receive long-term therapy to avoid esophageal fibrosis. Eosinophilic fibrosis occurs as a consequence of tissue remodeling. As discussed earlier in the chapter, asthma has been used as a model to understand EoE. These principles are used to understand the mediators responsible for remodeling in EoE. For example, IL-5 and IL-13 have shown to increase collagen in animal models.[43, 51, 132, 133] In addition, other mediators including periostin, TGF-β1, TSLP, Smad 3, and Siglec-F that have been studied in EoE pathogenesis are involved

in tissue remodeling through multiple mechanisms.[43, 51, 134, 135] The mast cell-eosinophil interaction has also shown to be important in the disease process. Mast cells are also producers of the mediators and cytokines responsible for pathogenesis of EoE, including TGF β 1. Eosinophils produce factors such as IL-9 that work in mast cell survival and recruitment. Mast cells and eosinophils are both found in esophageal biopsies of EoE models. Murine models with mast cell deficient mice show decrease in smooth muscle hypertrophy and proliferation. Therefore indicating that mast cells may play a role in fibrosis and also esophageal dysmotility in EoE.[55, 134, 136]

10. Future therapies

Treatment research is focused on understanding the mechanism behind the effectiveness of dietary and steroid therapy. In addition, therapy directed at specific mediators in the pathogenesis of EoE are also of great interest. Currently clinical trials are being conducted to find effective non-steroidal therapy. Anti-IL-5, anti-IL-13, and a CRTH2 receptor antagonist therapies are being studied in placebo controlled trials in adult and pediatric EoE patients and they have all shown that they can induce significant decreases in number of esophageal eosinophils compared to placebo.[137-141] However, their ability to resolve symptoms has not been repeatedly demonstrated. An IL-4 α -subunit antagonist is showing promise in asthma patients and may be a potential therapy for EoE.[142-144] As our knowledge of the immune pathways associated with EoE increase then other receptors could also be targets for therapies.

Eosinophilic esophagitis is a chronic immune mediated disease of the gastrointestinal tract. The diagnosis of the disease and its' subsequent treatment requires the expertise of the allergist/immunologist and the gastroenterologist. Allergists have a unique understanding of the pathophysiology of atopic diseases. The diagnosis of EoE is likely to occur at the time of atopic evaluation at an allergy clinic. The allergist can be of great assistance to the gastroenterologist in assessing food allergic individuals. In addition, allergists are in a position to identify and treat, with immunotherapy or biologics, pollen associated EoE. In our center a multi-disciplinary approach with GI and A/I has produced better outcomes for symptom response and overall improvement of disease compared to a fragmented approach to care (abstract accepted). The allergist needs to be able identify atopic patients who have risk for eosinophilic esophagitis. Likewise, the gastroenterologist who encounters a patient with food impaction and discovers esophageal eosinophilia should consult an allergist for potential triggers and possible joint treatment approaches. A cooperative multi-disciplinary clinic allows for coordinated food introductions with endoscopic follow-up evaluation. In addition, allergists routinely educate patients regarding food avoidance, sources of contamination and cross-reactivity. This type of detailed education has been a proven asset to dietary compliance. Allergists will also have the experience with biologics, such as anti-IL5 and anti-IL-4 monoclonal antibodies, which may not be currently used in gastroenterology practices.

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