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NARRATIVE REVIEW

Examining the Role of Type 2 Inflammation in Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic type 2 inflammatory disease characterized by an eosinophilic inflammatory infiltrate in the esophagus, leading to remodeling, stricture formation, and fibrosis. Triggered by food and aeroallergens, type 2 cytokines interleukin (IL)-4, IL-13, IL-5 produced by CD4+ T helper 2 cells (Th2), eosinophils, mast cells, basophils, and type 2 innate lymphoid cells alter the esophageal epithelial barrier and increase inflammatory cell tissue infiltration. Clustering analysis based on the expression of type 2 inflammatory genes demonstrated the diversity of EoE endotypes. Despite the availability of treatment options for patients with EoE, which include dietary restriction, proton pump inhibitors, swallowed topical steroids, and esophageal dilation, there are still no Food and Drug Administration–approved medications for this disease; as such, there are clear unmet medical needs for these patients. A number of novel biologic therapies currently in clinical trials represent a promising avenue for targeted therapeutic approaches in EoE. This review summarizes our current knowledge on the role of type 2 inflammatory cells and mediators in EoE disease pathogenesis, as well as the future treatment landscape targeting underlying inflammation in EoE.

Keywords: Eosinophilic Esophagitis; Eosinophils; Endotypes; Type 2 Inflammation

Introduction

Eosinophilic esophagitis (EoE) is a chronic type 2 inflammatory disease characterized by eosinophilic inflammation of the esophagus, epithelial barrier dysfunction, and esophageal subepithelial fibrosis.[1–3] In addition to symptoms related to esophageal dysfunction, a diagnosis of EoE requires the presence of ≥15 eosinophils/high-power field in the esophageal mucosa in the absence of other potential causes of esophageal eosinophilia.[1]

Although eosinophils are the histologic diagnostic feature of EoE, multiple immune cell types likely contribute to the complex mechanisms underlying EoE pathophysiology. EoE is characterized by epithelial barrier dysfunction in response to food antigens, leading to immune dysfunction and inflammation involving the type 2 inflammatory cytokines interleukin (IL)-4, IL-5, and IL-13.[4] This response is initiated by the processing and presentation of foreign (food) antigens by antigen-presenting cells (APCs) to adaptive immune cells such as naïve Th cells, leading to their polarization to effector cells. Dendritic cells are a major type of APC, and Langerhans cells, a type of dendritic cell found in squamous epithelia, appear to play a role in driving the type 2 inflammation characteristic of EoE. The downstream release of type 2 cytokines drives a positive feedback loop, promoting further inflammation and epithelial barrier dysfunction, ultimately resulting in persistent esophageal inflammation and the characteristic pathophysiologic features of EoE (such as esophageal fibrosis and tissue remodeling), as well as clinical symptoms of EoE (such as dysphagia, food impaction, and chest pain in adults and reflux, failure to thrive, and food refusal in children).[5–12] Persistent symptoms associated with EoE have a substantial impact on patient quality of life, and current treatment options are characterized by variable success rates.[13–15]

Although EoE is predominantly triggered by a type 2 response, other non–type 2 inflammatory factors (including

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Abbreviations used in this paper: CAPN14, calpain 14; CCL, C-C motif ligand; EMT, epithelial mesenchymal transition; EoE, eosinophilic esophagitis; IL, interleukin; ILC2, type 2 innate lymphoid cells; Ig, immunoglobulin; mRNA, messenger RNA; Siglec8, sialic acid–binding Ig-like lectin 8; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor beta; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

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interferon and tumor necrosis factor family member signaling) have also been implicated in EoE.[16,17] Given its predominance in EoE pathogenesis, this review will focus on the underlying mechanisms associated with type 2 inflammation in EoE.

With new targeted therapies in development for the treatment of EoE, better understanding of the underlying disease pathophysiology and the phenotypes and endotypes associated with type 2 inflammation offers the potential for precision medicine approaches in EoE. In this review, we summarize our current understanding of the roles of various type 2 inflammatory cells and cytokines in the pathophysiology of EoE and review the prospective treatment landscape targeting type 2 inflammation in EoE.

Type 2 Inflammation in EoE

The immune system is comprised of 2 parts (innate and adaptive) in which the innate immune system acts as a rapid, nonspecific first line of defense against pathogens and environmental insults, followed temporally by the adaptive system, which acts with specificity to provide a more robust and targeted response. The type 1 vs type 2 immunity paradigm was first described in the context of cytokine production from the adaptive T helper 1 (Th1) and T helper 2 (Th2) cell subsets.[18] It is now appreciated that the type 1/type 2 paradigm is larger than T cell subsets: type 1 immunity involves interferon-γ production from both innate and adaptive immune cells; type 2 inflammation is driven by the activity of key type 2 cytokines IL-4, IL-5, and IL-13, which are produced by the adaptive and innate arms of the immune system, including Th2 cells, type 2 innate lymphoid cells (ILC2s), mast cells, basophils, and eosinophils, through shared cellular and gene transcriptional activation domains such as GATA-3 transcription factor.[19–28]

Type 2 inflammation in patients with EoE is characterized by elevated levels of type 2 cytokines IL-4, IL-5, and IL-13[29,30] and chemokines such as eotaxin-3 (Table 1).[29,46] In addition to the presence of eosinophils, elevated levels of Th2, ILC2s, basophils, and mast cells have also been detected in esophageal biopsies from patients with EoE.[26,30,36,46–48] Furthermore, locally elevated levels of immunoglobulin (Ig) E and IgG4 to shared antigens have also been found in EoE patients.[49,50] Despite the antigen-driven process associated with EoE that includes IgE-mediated allergic comorbidities, non-IgE-mediated type 2 inflammatory pathways are now recognized as playing pivotal roles in EoE pathogenesis.[2,3,51]

Characterization of Endotypes in EoE

Three distinct endotypes of EoE, with differing levels of type 2 inflammation, have been described in a multisite cross-sectional study of differential gene expression patterns in esophageal biopsies using the esophagitis diagnostic panel.[52] Endotype 1 is characterized by a normal endoscopic appearance, usually steroid sensitive, and has normal levels of type 2 inflammation hallmarks, classified as Th2 low; endotype 2 is seen primarily in pediatric patients and is associated with atopy, lack of a steroid response, and upregulation of pro-inflammatory cytokines (eg, IL-4 and thymic stromal lymphopoietin [TSLP]), classified as Th2 high; endotype 3 is seen primarily in adults, is non-atopic, is associated with fibrostenosis and narrow-caliber esophagus, and is associated with low expression of genes controlling epithelial differentiation, classified as Th2 intermediate (Figure). In a separate study, 5 subgroups of patients with active EoE were identified by unsupervised clustering based on the expression of the type 2 inflammatory genes *IL4*, *IL5*, *IL13*, C-C motif ligand (*CCL*)*26*, *TSLP*, Charcot-Leyden crystal, C-C motif chemokine receptor 3, and carboxypeptidase A3.[31] Group V patients had the highest expression of *IL5*, *TSLP*, *CCL26*, and genes associated with tissue remodeling; *IL5* and *IL13* were highly expressed in group IV; groups II and III had intermediate expression of *IL5* and carboxypeptidase A3, with high *TSLP* and *IL13* in group III.[31] The 5 groups varied not only by the expression of type 2 inflammatory genes but also in terms of membership in EoE endotypes 1–3 (Figure). Interestingly, the 3 endotypes had similar levels of esophageal eosinophils, indicating an apparent disconnect between the level of type 2 inflammation and number of eosinophils infiltrating the esophagus[31]; this represents a challenge to the clinician in terms of personalizing and optimizing treatment. As these endotypes suggest, heterogenous type 2 gene expression is observed in patients with EoE as a whole; however, the degree of type 2 gene overexpression is not directly correlated with the severity of disease features as defined by peak esophageal eosinophil count (Figure).[31] These findings may drive the variable responses to currently available therapies and to targeted biologic therapy, emphasizing the clinical importance of understanding the endotypes associated with the type 2 inflammatory pathophysiology of EoE.

There are several lines of evidence to support the paradigm that these endotypes and their associated clinical phenotypes may reflect the natural history of EoE, although further understanding is required to determine how these may be positioned within EoE classification. Distinct differences in clinical presentation and endoscopic findings are seen in pediatric vs adult EoE patients.[53,54] One study revealed that endoscopically defined inflammatory, fibrostenotic, and mixed EoE phenotypes were associated with distinct clinical characteristics and symptomatology and that for every 10-year increase in age, the odds of having a fibrostenotic phenotype more than doubles.[55] It is noted, however, that interpretation of this study is limited, given its retrospective nature, which by design only included patients who followed up. The association of fibrostenosis with age suggests that the natural history of EoE may be a progression from an inflammatory to a fibrostenotic disease. However, not all patients may progress at the same rate, and this progression may be related more to the duration of

Table 1. Key Type 2 Cytokines and Chemokines and Their Role in EoE

Inflammatory mediator	Proposed role in EoE	Citation
IL-4	Differentiation of Th2 cells; secretion of eotaxin-3; B cell class switching to IgE; proliferation and activation of mast cells	Dunn 2020[31]; Swain 1990[32]; Cheng 2013[33]; Moore 2002[34]; McLeod 2015[35]; Noti 2013[36]
IL-5	Involved in eosinophil development, activation, survival, and recruitment; promotes tissue remodeling	Kouro 2009[37]; Mishra 2008[38]
IL-13	Promotes Th2 effector responses; involved in B cell class switching to IgE; eosinophil recruitment; mediates impaired epithelial architecture and barrier dysfunction	Cheng 2013[33]; Muir 2019[9]; Aceves 2010[5]; Blanchard 2007[39]; Ryu 2020[40]
IL-25	Produced by epithelial cells in response to environmental trigger; activates ILC2s	Camelo 2017[41]
IL-33	Produced by epithelial cells in response to environmental trigger; activates ILC2s	Camelo 2017[41]
Periostin	Promotion of eosinophil chemotaxis	Blanchard 2008[42]
Eotaxin-3/CCL26	Eosinophil chemoattractant	Blanchard 2011[29]
TSLP	Produced by epithelial cells in response to environmental trigger; activates ILC2s; mediates basophil response	Camelo 2017[41]
Eosinophils	Present in esophageal mucosa in EoE; release of eosinophil-associated proteins, including IL-4, IL-13, IL-5, TGF-β, T NFα, and IL-1β amphiregulin and osteopontin; potentially contribute to fibrosis	Straumann 2005[43]; Doyle 2020[44]
Mast cells	Release inflammatory mediators, including type 2 cytokines, TGF-β, histamines, and proteases; contribute to smooth muscle dysfunction	Aceves 2010[5]; McLeod 2015[35]; Ryu 2020[40]
Th2 cells	Produce of type 2 inflammatory cytokines IL-4, IL-5, IL-13	Wen 2019[45]; Cianferoni 2018[30]
Type 2 innate lymphoid cells (ILC2s)	Produce high levels of L-5 and IL-13; potential role in steroid resistance	Doherty 2015[26]

CCL26, C-C motif chemokine ligand 26; EoE, eosinophilic esophagitis; Ig, immunoglobulin; IL, interleukin; TGF-β, transforming growth factor beta; Th2, T helper cell type 2; TSLP, thymic stromal lymphopoietin.

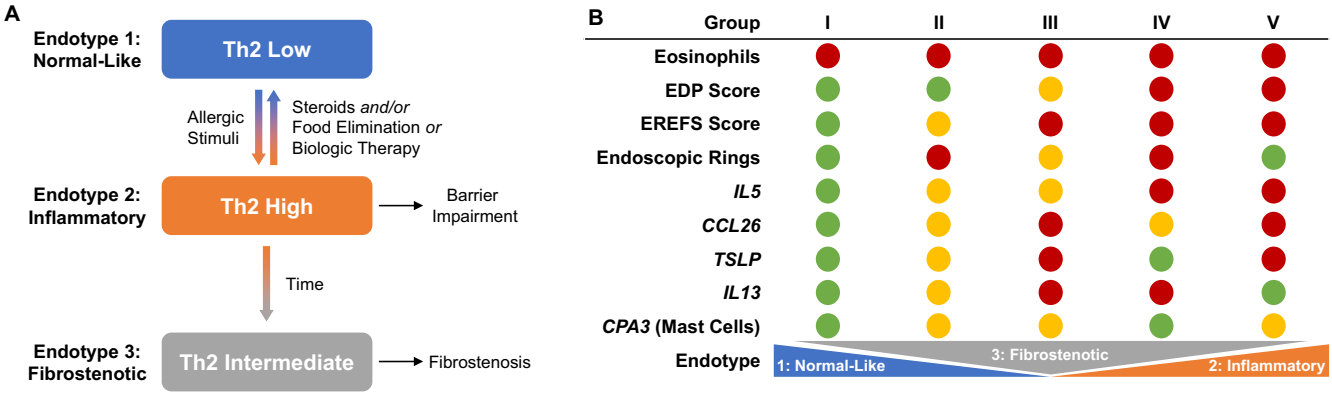

Figure. Endotypes of eosinophilic esophagitis and their characteristic features. (A) Model depicting patient progression from Th2-low phenotype (endotype 1) to a Th2-high phenotype (endotype 2) following allergic or inflammatory insult. On steroid treatment, food elimination, or biologic therapy the Th2-gene expression decreases and patients either resolve inflammation by reverting to a Th2-low phenotype or develop a fibrostenotic (endotype 3) signature. (B) Five subgroups of patients with active EoE were identified based on a variety of criteria, including expression of *IL5*, *IL13*, *CCL26*, *TSLP*, and *CPA3*. Relative levels of each criterion are reported in red (high), yellow (intermediate), or green (low). The 5 groups differed in the EoE endotypes spanned, but not in eosinophil levels, which were universally high. Group V patients had the highest expression of *IL5*, *TSLP*, *CCL26*, and genes associated with tissue remodeling. Groups II and III (which exhibited intermediate expression of *IL5* and *CPA3*) were differentiated by high *TSLP* and *IL13* in group III. CCL26, C-C motif chemokine ligand 26; EDP, eosinophilic esophagitis diagnostic panel; EREFS, endoscopic reference score; Th2, T helper cell type 2; TSLP, thymic stromal lymphopoietin (Adapted from J Allergy Clin Immunol: 2020;145:1629–1640.e4.).[31]

untreated disease than age,[56] underscoring the potential importance of rapidly and efficaciously bringing inflammation under control. This concept remains to be further investigated with prospective longitudinal studies.

Role of Key Type 2 Effector Cells and Inflammatory Mediators in the Pathophysiological Features of EoE

Eosinophils and Mast Cells. Eosinophils and mast cells are type 2 effector cells that are similar yet distinct classes of granulocytes, serving critical roles in allergic inflammation.[20] Eosinophils and mast cells are both found in the esophageal epithelium of patients with EoE (Table 1) and can persist in some patients despite clinical remission.[43,57,58] When activated, both eosinophils and mast cells degranulate to release pro-inflammatory mediators (particularly type 2 cytokines) that can contribute to inflammation, remodeling, and fibrosis when dysregulated (Table 1).[40,44,59]

The critical role of eosinophils as a mediator of EoE pathophysiology has been demonstrated by several transgenic murine models. Notably, greater basal layer thickening and increased collagen deposition were observed in the epithelial mucosa and lamina propria of mice with experimental EoE compared with experimental controls. Conversely, eosinophil-deficient mice have significantly reduced the thickening of the basal layer and lamina propria collagen and do not develop esophageal strictures.[38,60] Further support for the role played by eosinophils comes from models of egg-induced EoE. These have demonstrated that inhibition of AMCase, an innate immune modulator, or sialic acid–binding immunoglobulin-like lectin (Siglec), a receptor highly expressed by eosinophils, reduces eosinophilic inflammation and esophagus remodeling.[61,62] In addition, evidence from an allergen-induced mouse model of EoE demonstrated that mast cells increase under inflammatory conditions, but esophageal eosinophil recruitment was not dependent on the presence of mast cells.[63] In addition, mice genetically deficient in mast cells were protected from smooth muscle cell hyperplasia in this model, suggesting that mast cells may impact peristaltic function in EoE.[63]

Although eosinophils are a defining feature of EoE histopathology,[1,3] peripheral blood eosinophils do not correlate with esophageal eosinophil counts or disease activity. Furthermore, there is a well-described discrepancy between peak esophageal eosinophil counts and symptom severity in adults,[64,65] although this may not be the case in children.[66] Other measures of disease severity, such as the level of esophageal fibrosis, have been correlated with the extent of esophageal eosinophilic degranulation rather than eosinophil count.[67] These observations are important for the clinician who is looking for objective measures to guide clinical decision-making. In addition, given the lack of association between eosinophils and symptomatology, other factors clearly contribute to this observation.

Type 2 Innate Lymphoid Cells and T Helper 2 Cells. The type 2 inflammatory cascade in EoE is thought to begin with environmental triggers such as food and/or aero antigens, resulting in epithelial release of the inflammatory alarmin molecules TSLP, IL-25, and IL-33; these in turn activate ILC2s and promote Th2 cell differentiation via effects on APCs, resulting in IL-4, IL-13, and IL-5 production (Table 1).[26,39,68,69]

Th2 cells are the dominant population of T cells in EoE pathology, expressing high levels of IL-13, IL-4, and IL-5 (Table 1).[45] ILC2s express high levels of IL-13 and IL-5 (Table 1), are highly enriched in biopsies of patients with active EoE, and are positively correlated with esophageal eosinophil counts.[26] Interestingly, the production of IL-5 and IL-13 from ILC2s is not sensitive to steroid inhibition and may provide mechanistic insight into steroid resistance in some EoE patients.[23] These Th2- and ILC2-derived type 2 inflammatory cytokines drive a positive feedback loop to promote further inflammation and epithelial barrier dysfunction (Table 1).[11,59]

IL-4 and IL-13. IL-4 and IL-13 are key and central mediators of type 2 inflammation affecting a range of inflammatory cells and downstream mediators (Table 1).[4,5,9,20,21,26,35,36,41,47,70–75] IL-4 and IL-13 share some overlapping features because of shared receptor signaling. The type I heterodimeric IL-4 receptor is comprised of the IL-4Rα subunit paired with the common γ chain, expressed largely on hematopoietic cells. However, IL-4, as well as IL-13, can signal through the type II heterodimeric receptor, the IL-4Rα subunit paired with IL-13Rα1, expressed on nonhematopoietic cells.[76] A second receptor for IL-13 is IL-13Rα2, previously thought to be a decoy receptor.[77] Multiple cell types express IL-4Rα, including mast cells, eosinophils, macrophages, lymphocytes, and epithelial cells. IL-4 and 13 signaling through IL-4Rα activates signal transducer and activator of transcription 6 (STAT6), contributing to Th2 effector function and the production of type 2 cytokines IL-4, IL-5, and IL-13 through GATA3.[19,32,78]

Both IL-4 and IL-13 upregulate the expression of chemokines, such as eotaxin-3 and periostin, which promote migration and trafficking of inflammatory cells, including eosinophils, to the site of inflammation, contributing to additional inflammatory infiltrate, cytokine production, and tissue remodeling and fibrosis in the context of EoE (Table 1).[4,20,23,79] IL-4 and IL-13 also contribute to B cell class switching to IgE,[49] leading to mast cell and basophil degranulation and the resulting release of pro-inflammatory mediators.[4,20,35,36,47,72–74] In addition, IL-4 directly activates mast cells leading to their enhanced proliferation and survival, increased type 2 cytokine production, and enhanced mast cell degranulation (Table 1).[35,36] There may also be a role for basophil-derived IL-4 in eosinophil infiltration into tissue.[79] Elevated IL-4 is observed in blood, in esophageal biopsies, and in esophageal T cells from patients with EoE,[31,39,45,59] highlighting the potential role of this cytokine

in EoE pathogenesis, and suggesting IL-4-targeted therapies may be promising for treatment of EoE.

IL-13 plays a critical role in tissue remodeling, fibrosis, and smooth muscle contractility in EoE, mediated largely through effects on epithelial cells, including the induced expression of proteases and matrix proteins (Table 1).[4,5,9,33] IL-13 contributes to impaired epithelial architecture and barrier dysfunction by inducing calpain 14 (CAPN14), an intracellular calcium-activated protease, more than 100-fold in esophageal epithelial cells.[4] CAPN14 overexpression is associated with impaired epithelial architecture and barrier dysfunction,[80] and CAPN14 genetic variants are implicated in very early onset EoE.[81] In fibroblasts, IL-13 induces the expression of matrix proteins, including collagen, matrix metalloproteases, and periostin.[33] IL-13 may also mediate barrier function by downregulating *DSG-1*, *filaggrin*, and *involucrin* genes important for epithelial integrity.[40] Finally, IL-13 promotes epithelial mesenchymal transition (EMT), a process in which polarized epithelial cells transition to a mesenchymal cell phenotype, via transforming growth factor beta (TGF-β), contributing to tissue fibrosis in the context of chronic inflammation.[9,33] The process of EMT contributes to the subepithelial fibrosis characteristic of EoE, and in esophageal biopsies from EoE patients, EMT is correlated with the presence of eosinophils and eosinophil peroxidase, TGF-β, and fibrosis.[82]

In vivo data support IL-13 as a promising therapeutic target in EoE. IL-13 antibody blockade reduces esophageal eosinophilia in these models.[83–86] Intratracheal delivery of recombinant IL-13 induces epithelial hyperplasia in the esophagus in a manner dependent on both STAT6 and IL-5.[86] In mouse models of allergen-induced EoE, mice genetically deficient in IL-13, IL-5, or STAT6 were at least partially protected from disease.[83]

Real-world evidence also supports a role for IL-13 in EoE pathogenesis. IL-13 messenger RNA (mRNA) levels are increased in esophageal biopsies from EoE patients compared with healthy controls,[39] and IL-13 expression is significantly elevated in activated eosinophils in the esophagus and intestine of patients with EoE.[43] Experimentally, IL-13 stimulation of esophageal epithelial cells in vitro induces an EoE-specific esophageal transcriptome very similar to that observed in biopsies from EoE patients, suggesting that IL-13 is a fundamental regulator of EoE.[39] Both increased IL-13 levels and the EoE transcriptome are largely reversible after steroid treatment in vivo, which acts as a global, nonspecific suppressor of inflammation.[39]

Taken together, the evidence presented here implicates IL-13 as an important driver of epithelial barrier dysfunction and fibrosis, driving esophageal dysfunction and food impaction, respectively.

Interleukin-5. Early in vitro studies indicated a role for IL-5 as an eosinophil-specific differentiation factor.[87] IL-5 is now appreciated as a critical factor in the maturation, differentiation, and survival of eosinophils.[37] IL-5 signals through a heterodimeric receptor, consisting of the IL-5Rα chain and the common β chain, to activate Janus kinase-STAT as well as phosphoinositide 3-kinase (extracellular signal-regulated kinase signaling pathways).[88] In humans, the IL-5Rα chain is expressed by eosinophils and basophils (Table 1).[37]

Mouse models support a role for IL-5 in EoE (Table 1).[38,89–91] Experimentally, overexpression of IL-5 in the esophagus leads to elevated local levels of IL-13 and eotaxin-1.[89] Transgenic mice overexpressing IL-5 in T cells have an eosinophilic infiltrate in the esophagus that recapitulates features of human disease such as strictures, supporting a role for IL-5 in fibrostenosis.[90,91] In an allergen-induced mouse model of EoE, IL-5-mediated eosinophilia promoted tissue remodeling of the esophagus, including collagen deposition in the mucosa and lamina propria, and thickening of the basal layer.[38]

Therefore, IL-5 presents another attractive therapeutic target. Data on the role of IL-5 in EoE in humans come largely from clinical trials, in which monoclonal antibodies were used to target IL-5 and its receptor. These monoclonal antibodies reduced total esophageal eosinophil counts, but clinical improvement was not consistently noted. However, these were studies undertaken before the development of validated patient report outcome measures.[92–95] The role of IL-5 as a therapeutic target is currently being investigated (NCT03656380).

Role of Other Inflammatory Mediators on the Pathophysiologic Features of EoE

Other mediators have been implicated in the type 2 inflammatory pathways contributing to the pathogenesis of EoE, including periostin, eotaxin-3, IgE, and the alarmin TSLP.

Periostin is an extracellular matrix protein largely produced by fibroblasts and epithelial cells, which can be induced by TGF-β and IL-13 (Table 1).[42] As a result of its interaction with extracellular matrix proteins, it may play a role in promoting eosinophil trafficking and adhesion.[59] In a mouse model of allergen-induced esophageal eosinophilia, mice genetically deficient in periostin had increased blood eosinophils levels and decreased eosinophils in the esophagus compared with controls, directly implicating periostin in eosinophil chemotaxis.[42] Although serum periostin levels are only slightly elevated in EoE patients compared with controls,[96] periostin expression is increased in the esophageal mucosa of active EoE patients.[97]

Eotaxin-3 (CCL26) is a potent eosinophil and mast cell chemoattractant (Table 1). In vitro, IL-4 and IL-13 can induce eotaxin-3 expression via STAT6 in esophageal epithelial cells.[33] Eotaxin-3 not only attracts eosinophils but also induces eosinophil activation and degranulation via MAP kinase activation.[98] Eotaxin signaling is required for the development of EoE in an experimental mouse model.[99] Eotaxin-3 is the most highly expressed gene in esophageal

tissue in patients with EoE relative to controls, and mRNA and protein levels of eotaxin-3 correlate with the number of eosinophils and mast cells in tissue.[99] Highlighting the importance of this protein, a single nucleotide polymorphism in the untranslated region of the eotaxin-3 gene is associated with susceptibility to EoE.[99] Esophageal eotaxin-3 mRNA level alone has an 89% sensitivity in distinguishing patients with and without EoE, and circulating eotaxin-3 levels correlate with esophageal eotaxin-3 expression, suggesting its potential utility as a diagnostic biomarker.[29,100]

The high concurrence of comorbid atopic conditions in EoE suggests a role for IgE in EoE pathophysiology.[101] However, experimental models indicate that EoE can develop in an IgE-independent manner, dependent instead on TSLP-elicited basophils.[36] The anti-IgE antibody omalizumab had limited clinical or histologic effects in EoE patients, further supporting only a peripheral role for IgE in directly impacting disease pathogenesis.[50]

TSLP is a cytokine expressed by epithelial cells and keratinocytes. TSLP can induce activated dendritic cells to express the co-stimulatory molecule OX-40 ligand, a member of the tumor necrosis factor superfamily, which is involved in interactions between dendritic cells and T cells. OX-40 ligand is thought to drive the subsequent polarization of naïve Th cells toward a type 2 phenotype.[102] TSLP also activates ILC2 cells, which also serve as important sources of IL-5 and IL-13 in the type 2 immune cascade (Table 1). TSLP can also induce basophils to express IL-4, particularly in the context of non-IgE type 2 inflammation.[59] Experimentally, TSLP mRNA expression can be induced in primary esophageal epithelial cells in response to toll-like receptor signaling, suggesting the esophageal epithelium is an important source of TSLP in EoE.[69] In a mouse model of food antigen-driven EoE, TSLP was required for the development of disease in a manner that was also dependent on basophils, suggesting a role for the TSLP-basophil axis in EoE development.[36] In this model, neutralizing antibodies to TSLP were also effective in treating established EoE.[36] TSLP levels are elevated in esophageal tissue from patients with EoE compared with controls,[36,103,104] and TSLP is highly expressed in esophageal epithelium in areas infiltrated by basophils.[105] TSLP therefore contributes to EoE pathophysiology by acting as an upstream regulator of type 2 inflammation and may also have potential as a biomarker.

Current Therapeutic Options for EoE

Current treatment options for EoE are limited and have variable rates of remission induction and long-term maintenance therapy.[13–15] Although treatment recommendations for eosinophilic esophagitis continue to evolve, first-line approaches in patients with EoE include dietary therapy, proton pump inhibitors (PPIs), and swallowed topical corticosteroids.[1,14,106] Endoscopic dilation of the esophagus is often performed on patients with advanced disease resulting in esophageal strictures or narrow-caliber esophagus. Dilation is used for stricturing disease, but it does not treat the underlying type 2 inflammation; therefore, repeat dilations may be required because of restricturing.[107] Understanding how each treatment impacts EoE pathophysiology is key to tailoring therapy to EoE patients of different phenotypes or endotypes to increase the chance of therapeutic success.

Dietary Therapy

Three main categories of dietary therapy have been described: elemental diets, consisting of exclusive feeding with nonallergenic, amino acid–based formulas[14,108]; empiric diets, based on removal of the 1, 2, 4, or 6 common food antigens (cow's milk, wheat, egg, soy, peanut/tree nuts, fish/shellfish)[109–112]; and specific food allergy test–directed elimination diets.[106] Specific food allergy testing using standard allergy tests for IgE-mediated reactions is poorly predictive of food triggers in EoE, making test-directed elimination diets the least effective dietary therapy option.[106] Dietary therapy can eliminate or prevent the need for chronic medication by identifying and removing trigger foods and reducing inflammation systemically rather than locally.[109] Although empiric dietary therapy options are generally effective in achieving and maintaining EoE remission, they can be challenging to maintain.

PPI Therapy

PPI therapy is effective in a subgroup of EoE patients that are clinically indistinguishable from non-PPI responsive patients,[113] with a reported pooled histologic response rate of 42%.[14] In responsive patients, PPI therapy is associated with reduced Th2 inflammation, gene expression,[114] and endoscopic features of fibrosis.[115] PPIs have been shown to inhibit Th2-induced eotaxin-3 mRNA and protein expression in esophageal epithelial cells in a mechanism dependent on STAT6,[33,116] highlighting a novel role for PPIs independent of gastric acid reduction.

Topical Corticosteroid Therapy

As in many chronic inflammatory conditions, steroids are a common and effective treatment for many EoE patients.[117] Swallowed topical corticosteroids induce histologic remission in approximately two-thirds of patients[14] and are generally well tolerated in both short- and long-term studies.[14,118,119] A meta-analysis demonstrated no clear trends in symptom reduction with topical steroids.[117] However, more recent studies report an improvement in dysphagia symptoms.[14,120] Topical corticosteroids may reverse remodeling due to edema or fibrosis; however, alleviation of established fibrosis may require mechanical dilation.[107,121]

EoE is a progressive disease, with long-term challenges that impact patients' health-related quality of life across multiple parameters. Repeated endoscopies, including those

Table 2. Novel Targeted Therapies for EoE

Drug	Target	MOA	Reference
Omalizumab	IgE	Lowers free IgE levels	Clayton 2014[50]
Mepolizumab	IL-5	Stops IL-5 from binding to its receptor on the surface of eosinophils and decreases eosinophil accumulation	Straumann 2010[92]; Assa'ad 2011[93]; Otani 2013[95]
Reslizumab	IL-5	Blocks IL-5 signaling on eosinophils and eosinophil accumulation	Spergel 2012[94]; Markowitz 2018[127]
Benralizumab	IL-5 receptor alpha	Blocks IL-5 signaling; induces eosinophil apoptosis via NK cell–mediated antibody-dependent cellular cytotoxicity	Bleecker 2016[128]; Kolbeck 2010[129]
Cendakimab (RPC4046)	IL-13	Binds to the IL-13 ligand, inhibits binding to IL-13Rα1 and IL-13Rα2 subunits	Hirano 2019[130]; Dellon 2021[119]
Dupilumab	IL-4 receptor alpha	Blocks signaling of IL-4 and IL-13 that contribute to type 2 inflammation in EoE	Hirano 2020[14]
Lirentelimab (AK002)	Siglec8	Blocks Siglec8 signaling, leading to eosinophil depletion and mast cell inhibition	Dellon 2020[131]
Etrasimod	S1P receptor	Modulates S1P receptor signaling to block lymphocyte trafficking to sites of inflammation	

S1P, sphingosine 1 phosphate; Siglec8, sialic acid–binding Ig-like lectin 8.

used to establish diagnosis and monitor response to therapy, involve considerable cost.[122] Although each of the currently available therapies is effective to a certain extent, or in a subgroup of patients, significant unmet needs remain, including the ability to predict who will respond to a given therapy, the role and safety of chronic maintenance therapy, and how best to approach patients who fail to respond to a given class of therapy. Importantly, many patients are unable to control their disease with currently available therapies, and significant variation in adherence to guidelines regarding treatment choice and assessment of response have been documented.[123–126]

Novel Targeted Therapies

A variety of novel therapies that target the underlying type 2 inflammatory pathophysiology of EoE detailed previously are now in various stages of development (Tables 1 and 2).

Clinical trials investigating the IL-5-targeting agents mepolizumab and reslizumab, commonly prescribed for asthma, support a role for IL-5 in terms of eosinophil accumulation in the epithelium, including in pediatric patients. However, only a small group of patients achieved complete histologic remission, and clinical improvement was inconsistent. Although mepolizumab and reslizumab were generally well tolerated, small patient numbers and a lack of control groups (only 2 studies were placebo controlled) preclude any definitive conclusions.[92–95] A randomized, placebo-controlled, phase 2 study of mepolizumab is currently ongoing (NCT03656380).

Benralizumab is a humanized anti-IL-5 receptor alpha monoclonal antibody used for the treatment of eosinophilic asthma.[128] Benralizumab acts by blocking IL-5 signaling and also by inducing eosinophil apoptosis via natural killercell–mediated antibody-dependent cellular cytotoxicity.[129] A randomized, placebo-controlled phase 3 trial of benralizumab in adults and adolescents with EoE without esophageal strictures preventing passage of a standard adult endoscope is currently ongoing (NCT04543409).

Given the important role of IL-13 in mediating tissue remodeling, fibrosis, and smooth muscle contractility (as discussed in the prior section), several studies have examined the targeting of IL-13 signaling.[14,119,130,132] In a placebo-controlled phase 2 trial, the anti-IL-13 antibody cendakimab (formerly RPC4046) reduced esophageal eosinophil counts and endoscopic and histologic scores at week 16 and week 52 in a long-term open-label extension analysis of adult patients with EoE without esophageal stricture preventing passage of a standard adult endoscope.[119,130] Importantly, comparable responses were observed in both nonsteroid-refractory and steroid-refractory subgroups, suggesting this biologic therapy may be beneficial to this group of patients who currently have no suitable pharmacological options. However, cendakimab did not reduce dysphagia symptom severity and frequency, although the study was not powered to assess these outcomes. Furthermore, the study is potentially limited by the inability of approximately 25% of patients to complete the 52-week long-term extension study. Cendakimab was well tolerated with a consistent safety profile across the induction and long-term extension periods. Most adverse events were mild or moderate, with upper respiratory tract infection (21%) and nasopharyngitis (14%) most commonly reported through week 52.[119,130] A randomized, double-blind, placebo-controlled phase 3 trial of this drug is currently ongoing (NCT04753697).

As both IL-4 and IL-13 upregulate the expression of chemokines that promote eosinophil migration to the site of inflammation, several studies have investigated the targeting of IL-4/13 signaling in patients with EoE.[14,133] In a randomized, placebo-controlled phase 2 trial dupilumab, a fully human monoclonal antibody that inhibits the signaling of the shared receptor component for IL-4 and IL-13, reduced dysphagia, histologic features of disease including esophageal eosinophils, and abnormal esophageal endoscopic features compared with placebo in adults with active EoE and without esophageal stricture preventing passage of a standard endoscope.[14] Dupilumab also increased esophageal distensibility, with reduced distensibility being associated with food impaction and need for dilation, and was generally well tolerated. The most common adverse events reported by patients who received dupilumab or placebo during the 12-week study period were nonserious injection-site erythema (35% and 8%, respectively) and nasopharyngitis (17% and 4%).[14,133] Data from the phase 3 LIBERTY-EoE-TREET study (NCT03633617) demonstrate that patients who received dupilumab achieved clinically meaningful improvements in histologic, symptomatic, and endoscopic aspects of EoE at week 24, which were sustained to week 52, with an acceptable safety profile.[134] Placebo-treated patients who switched to dupilumab experienced similar outcomes to dupilumab-treated patients. These findings were confirmed in a larger sample size of adolescents and adults with EoE.[135,136] In addition, a separate randomized, placebo-controlled phase 3 study in pediatric patients with active EoE (NCT04394351) is ongoing.

Lirentelimab, (AK002), is an investigational, monoclonal antibody targeting Siglec8, a cell-surface protein expressed exclusively on eosinophils and mast cells[131] that leads to eosinophil depletion and mast cell stabilization. In a recent phase 2 placebo-controlled trial of AK002 in adult patients with eosinophilic gastritis and/or eosinophilic duodenitis, a subset of patients had concurrent EoE that improved with therapy. Lirentelimab was well tolerated, although higher rates of mild-to-moderate infusion-related reactions were reported in the lirentelimab vs placebo group (60% vs 23%, respectively). Other common adverse events were flushing, feeling of warmth, and headache.[131] A randomized, placebo-controlled phase 2/3 trial evaluating lirentelimab in adults and adolescents with EoE is currently underway (NCT04322708).

Etrasimod is an investigational, oral selective sphingosine 1 phosphate receptor modulator being developed for the treatment of inflammatory and immune-mediated disease and acts, in part, by blocking lymphocyte trafficking to sites of inflammation. Etrasimod is being evaluated in a randomized, placebo-controlled phase 2 trial of adults with EoE (NCT04682639).

Evidence from clinical trials interrogating pathways of type 2 inflammation suggest that histologic improvement alone, that is, reduction in esophageal-associated eosinophils, may be insufficient to address the complex underlying pathophysiology of EoE and reduce clinical symptoms.[92–95] This may reflect differences in eosinophil homing vs activation vs differentiation.

Conclusion

EoE is a complex disease, with multiple phenotypes and endotypes emerging that are associated with type 2 inflammation and that may reflect the natural history of EoE disease progression. Although eosinophils are a hallmark feature of the disease, their roles in disease activity and progression remain unclear. Current treatment options, while effective for some patients, leave many with incompletely controlled disease and persistent symptoms. With promising therapeutic options in the pipeline, there is a need for a greater understanding of the underlying inflammatory pathophysiology of EoE and endotypes to enable precision medicine approaches and better tailor treatment for this complex and burdensome disease.

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