Review Article

EoE behaves as a unique Th2 disease: a narrative review

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Background and Objective: To highlight and interpret two significant differences between eosinophilic esophagitis (EoE), a type 2 helper cell (Th2) disease, and three other representative Th2 diseases. EoE, asthma, atopic dermatitis (AD), chronic rhinosinusitis (CRS) and other Th2 diseases employ epithelial alarmins to recognize triggers, share a prototypical inflammatory cascade, and respond to glucocorticoids. However, EoE also has several distinguishing characteristics which may be explained by a distinct pathophysiologic mechanism.

Methods: The following report consist of four related narrative reviews which combine comprehensive PubMed and Google searches. Two reviews were performed to identify and contrast all eligible studies describing serologic markers in EoE compared to asthma, AD, and CRS. Two additional reviews then compare the responses to parenteral biological therapies in EoE and in the same representative Th2 diseases.

Key Content and Findings: Comprehensive literature searches definitively differentiate the absence of serologic markers in EoE compared to their identification in the other representative Th2 diseases. Similarly, a summary of therapeutic trials demonstrates that while EoE is unable to clinically respond to a variety of parenteral biological therapies, asthma, AD and CRS are very effectively treated with this same approach. A novel pathophysiology for EoE is proposed, and the emerging literature that support its existence is summarized.

Conclusions: The fundamental properties described in this narrative regarding serologic signaling and response to parenteral therapy in EoE could be explained if EoE employs a unique application of the Th2 pathway. One potential mechanism consistent with these observations is that EoE employs exclusively esophageal mucosal constituents to initiate and generate the prototypical Th2 cascade and the fibrostenotic changes that follow.

Keywords: Eosinophilic esophagitis (EoE); type 2 helper cell diseases (Th2 diseases); serologic markers; biological therapy; narrative review; thymic stromal lymphopoietin (TSLP)

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Introduction

Eosinophilic esophagitis (EoE) is considered to be a type 2 helper cell (Th2) disease, a group that shares common pathophysiologic characteristics. However, EoE, unlike asthma, atopic dermatitis (AD), and chronic rhinosinusitis (CRS), has certain distinct behaviors which could potentially influence effective therapeutic approaches. The objective of the following narrative report is to organize the published references which clearly document two significant disparities. The conclusion then provides a possible explanation for these unique characteristics and the data that supports the proposal. A comprehensive search that demonstrates the absence of reliable serologic markers for EoE is contrasted to a second search highlighting the studies that identified markers for other representative Th2 disease. Subsequently, a third search is presented that documents the disappointing results of biological therapies in EoE. The final search includes longitudinal studies, clinical trials, meta-analyses and review articles describing the successful application of biological therapies for asthma, AD, and CRS. A potential explanation for these disparities is offered in the form of a unique Th2 pathway in EoE, along with the evidence that supports the existence of this same pathway in asthmatic epithelium.

Th2 diseases are initiated by the conversion of naive T cells to helper type 2 cells which then coordinate an inflammatory cascade in the setting of allergic, parasitic or neoplastic triggers. A characteristic inflammatory milieu is demonstrated in different Th2 conditions and includes a number of recurring players including IL-4, IL-5, IL-13, eotaxin and periostin (1). In patients with Th2 diseases, sensitizing triggers stimulate epithelial cells to secrete a group of cytokines, referred to as alarmins, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) (2). These alarmins oversee the immune response through their generation of Th2s and the activation of additional epithelial cells, dendritic cells, and other immune cells residing in the underlying mucosa (2).

EoE is the result of a dysregulated Th2 immune response to dietary and aeroallergens that yields exclusive esophageal inflammation and dysfunction. It shares the same triggers and downstream agents typically associated with other Th2 conditions, and similarly also responds to glucocorticoid therapy. This report focuses on the two unique characteristics of EoE described above. A novel pathway, recently proposed to be present in some asthmatics, is suggested as the mechanism for this disparity. The literature that supports this pathway in asthma and is consistent with its existence in EoE concludes the discussion. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-15/rc).

Methods—literature searches

The objective criteria which guided the preparation of the four tables that follow required that all included studies were: English language, peer reviewed, PubMed cited, IRB approved studies on children or adults or both with diagnosed Th2 diseases, that contained statistical analyses. The goal of the authors was to collate the studies that illustrate the perceived disparity between EoE and several other Th2 diseases through January 2022.

The initial conceptualization for the presented review was derived from review articles describing the consistently disappointing results of published EoE studies that (I) attempted to identify EoE serum markers (3,4) and (II) attempted to treat EoE with parenteral biological therapies (5-7). To examine more closely if other Th2 diseases faced the same problems, four comprehensive literature searches were then conducted through January 2022, to compare EoE and three other representative Th2 diseases (asthma, AD, and CRS).

Table 1 includes the eligible citations in the review articles on serologic markers in EoE (3,4) and adds more recent and any additional references that met our criteria. *Table 2* is an analogous review that collates studies that have successfully identified markers for asthma, AD and CRS based on reviews, respectively (54,56,57). *Table 3* includes all eligible studies included in the original review articles (5-7) describing attempts to treat EoE with parenteral biological therapies. These were then similarly updated and expanded through PubMed and Google searches. Analogously, *Table 4* includes the citations found in review articles describing therapeutic trials in the same three Th2 diseases. In addition to the references in these reviews, *Table 4* was then updated and augmented as described above.

Specifically, PubMed and Google searches for EoE serum biomarkers (*Table 1*) and the specific Th2 diseases (*Table 2*) employed combinations of the key words: name of serum biomarkers and either EoE, asthma, AD, or CRS. *Tables 3,4* were derived from combinations of EoE, asthma, AD, and CRS and the names of the listed biological therapy/biologics following the same criteria.

Table 1 Studies measuring serum levels of cytokines in EoE

Marker	Age group	Brief result	Ref No.
IL-5	Adult	Higher proportion of individuals with EoE *vs.* ctrl have higher than minimum detected levels	(8)
	Adult	No difference between EoE *vs.* ctrl	(9,10)
	Adult	No difference between EoE *vs.* non-EoE ctrl	(11)
	Pediatric	Higher in EoE *vs.* ctrl	(12)
	Pediatric	No difference between EoE *vs.* ctrl	(13-16)
	Pediatric	Higher in active EoE *vs.* healthy ctrl	(17)
		No difference between active *vs.* inactive EoE	
	Both	Lower in pre-treatment EoE *vs.* non-EoE ctrl	(18)
		No difference between pre- and post-treatment EoE	
	Both	No difference between EoE *vs.* ctrl	(19)
	Unknown	Higher in active EoE *vs.* GERD	(20)
		No difference between EoE *vs.* EoC/EoG or IBD or healthy ctrl	
IL-13	Adult	No difference between EoE *vs.* ctrl	(8,9)
	Adult	No difference between EoE *vs.* non-EoE ctrl	(11)
	Pediatric	Higher in EoE *vs.* ctrl	(12)
	Pediatric	No difference between EoE *vs.* ctrl	(16)
	Pediatric	Higher in EoE *vs.* ctrl.	(17)
		No difference between active EoE *vs.* inactive EoE	
	Both	No difference between EoE *vs.* ctrl	(19)
Eotaxin-3	Adult	No difference between EoE *vs.* ctrl	(8-10)
	Adult	No difference between EoE *vs.* non-EoE ctrl	(11)
	Pediatric	Higher in active EoE *vs.* healthy ctrl	(13)
		No difference between active EoE and inactive EoE	
	Pediatric	No difference between EoE *vs.* ctrl	(12)
	Both	No difference between EoE *vs.* ctrl	(18)
Periostin	Adult	Higher in active EoE than non-EoE ctrl	(21)
		No difference between pre- *vs.* post-treatment EoE	
TSLP	Adult	No difference between EoE *vs.* ctrl	(8-10)
	Pediatric	Higher in EoE *vs.* ctrl	(22)
IgG4	Adult	Higher in EoE *vs.* ctrl (both total and food specific IgG4)	(23)
	Adult	Total IgG4: no difference between EoE *vs.* ctrl	(24)
		Food specific IgG4: higher in EoE *vs.* ctrl	
	Pediatric	Total IgG4: no difference between EoE *vs.* ctrl	(25)
		Food specific IgG4: higher in EoE *vs.* ctrl	
ECP	Both	Increased in EoE *vs.* controls but did not decrease with steroids	(18)
15(S)-HETE	Pediatric	No difference between EoE *vs.* non-EoE ctrl	(16)
TGF-β1	Adult	Higher in EoE *vs.* non-EoE ctrl	(11)
MBP	Adult	Higher in EoE *vs.* non-EoE ctrl	(11)

This table lists 18 publications examining 38 combinations of the 10 listed markers, to determine if any were able to predict EoE. Twenty-two entries failed to show any correlation. Among the remaining 16 entries, only 7 were able to show correlations (non-italicized). EoE, eosinophilic esophagitis; IL, interleukin; Ctrl, control; GERD, Gastroesophageal reflux disease; EoC, eosinophilic colitis; EoG, eosinophilic gastritis; IBD, inflammatory bowel disease; TSLP, thymic stromal lymphopoietin; IgG4, immune globulin subclass 4; ECP, eosinophil cationic protein; HETE, hydroxyeicosatetraenoic acid; TGF-β1, transforming growth factor β1; MBP, major basic protein.

Table 2 Studies measuring serum levels of cytokines in other Th2 diseases

Diseases	Biomarkers	Brief results	Ref No.
Asthma	Eosinophil count	Lower level correlates with effectiveness to steroids	(26,27)
		Lower level correlates with effectiveness to biologics	(28-31)
		Higher level correlates with rate of severe exacerbations	(32,33)
		Higher level correlates with decline in lung function	(34)
	IgE	Higher in severe asthma *vs.* less severe asthma	(26,35,36)
	ECP	Correlates with severity. Systematic review of 53 publications	(37)
		Higher in acute *vs.* stable asthma or healthy ctrl in children	(38)
	Periostin	Higher in asthma *vs.* ctrl. Meta-analysis with 16 publications	(39)
		Biomarker for the prediction of lung function. Negatively correlated with FEV1/FVC in stable patients	(40-42)
	TSLP	Higher in asthma *vs.* ctrl	(43)
		Higher in steroid resistant *vs.* steroid sensitive asthma	(44)
CRS	Eosinophil count	Higher in eosinophilic *vs.* noneosinophilic subgroups	(45-48)
		Higher in pre-operative *vs.* post-operative eCRS	(49)
		Higher in those who need long term systemic steroid or biologics post-operatively	(50)
	EDN	Higher in eosinophilic *vs.* noneosinophilic subgroups	(51)
	ECP	Higher in eosinophilic *vs.* noneosinophilic subgroups	(51)
		Higher in CRS *vs.* healthy ctrl	(52)
	Periostin	Higher in severe eCRS *vs.* less severe eCRS or ctrl	(53)
		Higher in eosinophilic *vs.* noneosinophilic subgroups	(48)
AD	TARC	Correlates with disease severity in 4 longitudinal and 16 cross-sectional studies	(54)
	CTACK	Correlates with disease severity in 7 cross-sectional studies	(54)
	E-selectin	Correlates with disease severity in 4 longitudinal studies	(54)
	MCD	Correlates with disease severity in 5 cross-sectional and 2 longitudinal studies	(54)
	LDH	Correlates with disease severity in 4 cross-sectional studies.	(54)
	IL-18	Correlates with severity in 6 cross-sectional studies and 1 longitudinal study	(54)
	TSLP	Higher in both atopic *vs.* non-atopic eczema *vs.* ctrl	(55)
		No differences in atopic *vs.* non-atopic eczema	

This table includes over 30 publications investigating serologic biomarker levels in other Th2 diseases (asthma, rhinosinusitis, and AD). The markers were able to predict presence of the disease, and/or the severity of the disease. For AD, references that analyze multiple previously published randomized control trials have been included. Th2, type 2 helper cell; IgE, immunoglobulin E; ECP, eosinophil cationic protein; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TSLP, thymic stromal lymphopoietin; ctrl, control; CRS, chronic rhinosinusitis; END, eosinophil-derived neurotoxin; eCRS, eosinophilic chronic rhinosinusitis; AD, atopic dermatitis; TARC, thymus and activation-regulated chemokine; CTACK, cutaneous T-cell attracting chemokine; MCD, macrophage-derived chemokine; LDH, lactate dehydrogenase; IL, interleukin.

All references were reviewed by two authors (LY, SSR) to verify that all of the marker studies in *Tables 1*,*2* met all of the above criteria and contained statistical analysis for at least one of the markers. When more than one marker was measured, they were each noted in the tables. The same authors reviewed all of the studies included in *Tables 3*,*4* to

Table 3 Summary of biologic agents studied as potential EoE treatment

Target	Biologics	Age group	Brief results	Ref No.
IL-5	Mepolizumab	Adult	4 patients reduced tissue eos (but all >20 eos/hpf and improved quality of life pre- *vs.* post-treatment	(58)
		Adult	5 patients reduced tissue eos (but all >30 eos/hpf) and blood eosinophils *vs.* placebo	(59)
			No improvement in pathology and symptoms *vs.* placebo	
		Pediatric	Reduced tissue and blood eosinophils pre- *vs.* post-treatment	(60)
			No improvement in symptoms pre- *vs.* post-treatment	
	Reslizumab	Pediatric	Reduced tissue eosinophils *vs.* placebo	(61)
			No improvement in symptoms *vs.* placebo	
		Pediatric	Reduced tissue eosinophils and improved symptoms *vs.* placebo	(62)
IgE	Omalizumab	Pediatric	One-case report. No persistent improvement in neither symptoms nor pathology during the treatment	(63)
		Pediatric	Two-case report	(64)
			Improved clinical symptoms pre- *vs.* post-treatment	
			No change in endoscopy and histology findings pre- *vs.* post-treatment	
		Both	Reduced tissue eosinophils and improved symptoms pre- *vs.* post-treatment	(65)
			No difference in blood eosinophils pre- *vs.* post-treatment	
		Both	No improvement in tissue eosinophils and symptoms *vs.* placebo	(23)
IL-13	QAX576	Adult	Reduced tissue eosinophils *vs.* placebo	(66)
			No difference in dysphagia *vs.* placebo	
	RPC4046	Adult	Reduced disease activity grossly (EREFS), histologically (EoEHSS) but not dysphagia *vs.* placebo	(67,68)
IL-13 & IL-4	Dupilumab	Adult	Reduced disease endoscopically (EREFS), histologically (EoEHSS) and clinically (SDI-PRO score) *vs.* placebo	(69)
TNF-α	Infliximab	Adult	Three-case report	(70)
			No improvement in pathology, and heterogeneous clinical response pre- and post-treatment	

This table lists 14 publications evaluating the efficacy of 8 biologic agents. Several anti-IL5 studies showed improved histology but only one demonstrated histologic remission and clinical improvement. Three recent studies on IL13 directed therapy have shown improved eosinophilia but only dupilumab was also able to decrease symptoms. The remaining 9 studies failed to show meaningful therapeutic responses. EoE, eosinophilic esophagitis; IL, interleukin; eos, eosinophils; hpf, high power field; IgE, immunoglobulin E; EREFS, EoE endoscopic reference score; EoEHSS, eosinophilic esophagitis histologic scoring system; SDI-PRO, Straumann dysphagia instrument-patient reported outcome score; TNF-α, tumor necrosis factor alpha.

determine the relevance of the specific variables that were compared pre and post biologic therapy. *Table 4* includes a number of review articles, meta-analyses, and longitudinal studies that cited a number of individual studies. Only the aggregated reference and the final overall conclusions were included in the tables. All of the articles cited in all of the tables are referenced so that readers can refer to them for additional information. Additional details are included in *Table 5* and Table S1 which contains the search strategy followed by the search terms employed in this narrative

Table 4 Summary of biologic agents studied as potential Th2 disease treatments

Diseases	Biologicals	Brief results	Ref No.
Asthma	Mepolizumab; benralizumab; dupilumab; omalizumab; reslizumab	Reduction in exacerbations improved quality of life *vs.* standard therapy. Systematic Review including 28 publications and 19 randomized controlled trial	(71)
	Tezepelumab	Less asthma exacerbations *vs.* placebo	(72)
	Dupilumab;	Lower severe exacerbation rates *vs.* placebo	(73)
CRS	Mepolizumab	Reduced need in surgery *vs.* placebo	(74)
		Improved nasal polyp score and imaging *vs.* placebo	(75)
	Omalizumab	Improved in the Sino-Nasal Outcome *vs.* placebo	(76)
		Improved in total nasal endoscopic polyp scores, airway symptoms and quality-of-life *vs.* placebo	(77)
	Dupilumab	Improved Sino-Nasal Outcome and sense of smell *vs.* placebo	(78)
AD	Dupilumab	Improved SCORAD, EASI, pruritus, sleep, anxiety/depression *vs.* placebo. Systematic review of seven studies	(79)
	Tralokinumab	Improved SCORAD, quality of life, pruritus *vs.* placebo	(80)
	Lebrikizumab	Improved EASI *vs.* placebo	(81)
	Fezakinumab	Improved SCORAD *vs.* placebo	(82)
	Nemolizumab	Improved pruritus and EASI *vs.* placebo	(83,84)

This table lists 10 biologic agents tested in three Th2 diseases (asthma, CRS and AD). Almost all showed clinical improvement. Biological agents: Anti-IL5 Ab: mepolizumab, reslizumab; Anti-IL5 receptor Ab: benralizumab; Anti-IL4 receptor Ab: dupilumab; Anti-IgE Ab: omalizumab; Anti-TSLP Ab: tezepelumab; Anti-IL13 Ab: tralokinumab, lebrikizumab; Anti-IL22 Ab: fezakinumab; Anti-IL31 receptor A Ab: nemolizumab. Th2, type 2 helper cell; CRS, chronic rhinosinusitis; AD, atopic dermatitis; SCORAD, scoring atopic dermatitis; EASI, Eczema Area and Severity Index.

Table 5 The search strategy summary

Items	Specification
Date of search	Initial search: 04/23/2020; most recent update: 01/21/2022
Databases	PubMed, Google Scholar
Search terms used	See Table S1
Timeframe	No specific time limitation on publishing date, but recent studies sought
Inclusion and exclusion criteria	Inclusion criteria:
	Biomarkers studied using human blood samples in one of the following: eosinophilic esophagitis; asthma; atopic dermatitis; chronic rhinosinusitis;
	Biological therapies studied in one of the following: eosinophilic esophagitis; asthma; atopic dermatitis; chronic rhinosinusitis
	Exclusion criteria:
	Animal study;
	Biomarker analyzed in tissue or body fluid other than blood;
	No statistical analysis included
Selection process	Initial criteria developed and preliminary search for *Table 1* performed by Dr. Rabinowitz. Formal comprehensive searches started by Dr. Yu with updates and modification by Dr. Rabinowitz and Dr. Yu

review. The scale for the assessment of narrative review articles (SANRA) of this article is 12 (85).

Discussion

Two recent review articles have summarized the published literature describing the many attempts to identify a serologic biomarker for EoE, and both concluded that none could be incorporated into guidelines or employed in routine clinical practice (3,4). An expanded list summarizing the investigations cited by the review articles, as well as additional studies, including those published after the review articles, are presented in *Table 1*. As previously concluded, none of the typical cytokines or interleukins associated with the Th2 cascade were consistently shown to be increased in a reproducible manner that could be employed to diagnose EoE. A single study listed in *Table 1* has suggested that the cytokine TGF-beta and the multifunctional adhesion protein, myelin basic protein (MBP) were elevated in a cohort of adult EoE patients compared to non EoE controls and will need to be replicated. In addition, one study has found that eosinophilic cationic protein (an eosinophil product) was increased in EoE patients *vs.* controls but only absolute eosinophil count could predict esophageal eosinophilia after topical steroid therapy for eight weeks (18). However, one of the serologic EoE review articles concluded that peripheral eosinophilia could not be effectively employed to diagnose or assess EoE (3). Experimental work in our lab has extended the range of potential biomarkers prospectively studied with the same negative results. In addition, none correlated with other parameters employed to quantitatively asses EoE (86).

This is in sharp contrast to the other three representative Th2 diseases studied. *Table 2* lists over 25 publications, including meta-analyses of asthma as well as multiple cross-sectional and longitudinal studies in AD, that document that these other diseases' activities correlate with peripheral eosinophilia and various other serologic markers. In the course of reviewing the articles contained in *Table 2*, it was clear that they studied heterogeneous patient populations, were performed by multiple investigators, and thus established the reproducibility of these associations. The authors of the present study have not found a single published reference that highlights or attempts to analyze or interpret the significance of this apparent disparity. The significance of having serologic markers in other Th2 diseases, but not in EoE is analyzed in the conclusion section below.

The potential significance to the lack of biomarkers is the observation that in asthma the benefit of treatments targeting type 2 cytokines is restricted to patients who have biomarkers of type 2 inflammation (2). This observation has relevance for EoE and *Table 3* includes a number of trials of biological agents in various populations of EoE patients that did not meet therapeutic goals. The vast majority of these studies were examining biological therapies that had shown efficacy for other Th2 diseases. One trial employing an anti-IgE reported benefit, but several other trials failed to reproduce this outcome. Only the recent trial of dupilumab, which combines both interleukin (IL)-4 and IL-13 inhibition, yielded histologic, endoscopic, and clinical (decreased dysphagia scores by a validated instrument) responses in EoE (69). As a consequence of these studies, as of this time there is not a single FDA approved therapy for EoE. However, dupilumab was recently granted orphan status.

These results are again in sharp contrast to the multiple studies that have demonstrated clinical efficacy for biological agents antagonizing interleukins, IgE, and other cytokines for asthma, AD, and CRS which are summarized in *Table 4*. For asthma and atopic dermatitis comprehensive reports based on a large number of individual trials and longitudinal studies clearly demonstrate the efficacy of these agents for these other Th2 diseases. As indicated above in the previous tables, these studies have been performed by multiple investigators in heterogeneous populations including several multicenter protocols. Despite substantial progress in the understanding of EoE, why this Th2 condition uniquely lacks a serologic marker and uncharacteristically does not respond to parenteral agents efficacious for conditions with similar pathogenesis, remain unanswered. In addition, why and how the inflammation of EoE is limited to the esophagus is another unexplained phenomenon.

Tables 1-4 establish that there is a distinct disparity between the lack of serologic markers and the response to parenteral therapy in EoE compared to these other Th2 diseases. Whereas this could be interpreted as multiple "negative studies" in EoE, the authors propose that a distinct pathophysiology accounts for this incongruity. In this model, EoE would represent a locally mediated application of the Th2 paradigm where esophageal epithelial alarmins, including TSLP (87), would have a vital initiating role. Esophageal TSLP is overexpressed in active EoE and has been identified through a genome wide association study (GWAS) as a likely EoE candidate gene (88). TSLP, and perhaps other epithelial alarmins, would be

released by esophageal epithelial cells after exposure to dietary and aeroallergens. TSLP acting as both an autocrine and paracrine agent, as previously noted in asthma (see below) would stimulate additional epithelial cells, dendritic cells and other immune cells residing in the esophageal mucosa to release IL-5, IL-13, and other cytokines. These would then initiate and perpetuate the Th2 inflammatory cascade and subsequent remodeling. EoE would thus be an autonomous condition driven solely by intrinsic esophageal epithelial and mucosal constituents.

The concept of EoE as a completely local disease is also consistent with studies investigating the mechanism of the consequential fibrostenoses noted in EoE (89). The esophageal mucosa of active EoE patients contains activated Th2 cells that secrete increased levels of the TNF-related cytokine LIGHT, an inflammatory cytokine that converts resident esophageal mucosal fibroblasts to the fibrostenosing phenotype. Furthermore, the activated fibroblasts were shown to migrate to the epithelium where they directly interact with eosinophils (89). *In vitro* studies utilizing esophageal biopsy tissue from EoE patients have demonstrated esophageal epithelial cell-esophageal fibroblast cross talk which yielded increased collagen synthesis as well as upregulation of mucosal Lysyl oxidase, a collagen cross-linking enzyme, believed to play a role in the EoE fibrostenosing phenotype (90).

This proposed immunologic pathway, which also explains why EoE is limited to the esophagus, employs parallel features from gastrointestinal endocrinology. Historically, it was felt that after secretion, all gastrointestinal peptide hormones were required to employ the circulatory system to reach their target tissues. It is now established that paracrine-based signaling, achieved by the diffusion of somatostatin from gastric D cells to neighboring G cells, is an essential component of gastric acid homeostasis in healthy and diseased states.

A good deal of published work has established a pivotal role for locally secreted TSLP in asthma, and other Th2 diseases (4,6,7,69,87). TSLP is an IL-7-like cytokine that exerts its biological activities by binding to a heterodimeric receptor complex composed of the IL-7 receptor α-chain and the TSLP receptor chain. Evidence supporting its role in a parallel, autonomous Th2 response in the bronchial epithelium of asthmatics is simultaneously emerging (91-93). TSLP is greatly upregulated and secreted by asthmatic bronchial epithelium in response to aeroallergens (91). It is increased in the bronchoalveolar lavage from asthmatic patients and its level correlates with worsening lung function in steroid resistant asthmatic children (92). *In vitro*, TSLP and IL-4 treated T cells from asthmatic children produce increased amounts of IL-5 and IL-13 (93). Together these and other studies support the principle that epithelial TSLP is capable of acting as a paracrine and autocrine agent to amplify its own production and to induce local production of enhanced Th2 downstream inflammatory cytokines such as IL-5 and IL-13 (91,93). TSLP secretion occurs in the asthmatic airway epithelium following exposure to aeroallergens. TSLP then polarizes dendritic cells to induce a type 2 inflammation state through expansion and activation of Th2 cells, innate lymphoid cells, basophils, and other immune cells residing in the bronchial mucosa (94-98). These and other studies have led researchers to consider TSLP as a "master regulator of type 2 immune responses" at the barrier surfaces of skin and the respiratory/gastrointestinal tract (93,97). TSLP has also been linked to the development, maintenance and progression of generalized atopy, including asthma and AD (99). In a mouse model employed to study the progression from AD to asthma (the so-called "atopic march"), TSLP was overexpressed in the skin of animals with AD. Genetically engineered mice with diminished TSLP had markedly less symptoms. Further investigations looking at the time course of these events suggest that the early exaggerated production of TSLP in acute AD skin lesions might be important for initiating the atopic march and that this may be not be mediated through serologic TSLP (100).

Besides initiating Th2 inflammation, TSLP plays an integral role in the pulmonary remodeling noted in asthmatics via activation of the human airway smooth muscle TSLP receptor (101). Activation results in migration and proliferation of these cells, enhanced release of proinflammatory mediators, and multiple cytoskeleton changes (101). TSLP is also increased in nasal polyps of patients with CRS (102). An additional potential mechanism for TSLP to influence susceptibility in multiple allergic diseases is through its regulation of basophil hematopoiesis to create a population of functionally distinct basophils that promote Th2 cytokine-mediated inflammation (103).

The major limitations in this study are that there may be effective serologic markers and/or parenteral therapies that will be identified in the future for EoE and for other Th2 diseases. Dupilumab may already be able to fulfill that criterion. There is also the potential that despite the efforts outlined above to identify all relevant articles that address these differences, significant publications that are

inconsistent with this argument may have been published but were not recognized by our search strategy. There may also be investigations that will fulfill these criteria, but the authors have not yet reported their results or have chosen to publish them in sources that are not listed in PubMed. In addition, as this investigation was limited to studies published in English, there may be international investigators that have reported in foreign language journals, that will be replicated in the future by trials that will be reported in English. Finally, while the disparities documented above may be accurate, there may be an alternative explanation from the one which is offered by the presented interpretation. It is the hope of the authors that this report focuses attention on this variance and leads to further discussions which can ultimately result in newer, more effective therapeutic approaches for patients with EoE.

Conclusions/summary

The presented narrative review attempts to establish that EoE, behaves differently than three other representative Th2 diseases. Specifically, EoE does not have any identified reliable serologic markers and does not respond to parenterally administered biological therapies that are quite effective in asthma, AD, and CRS. Rather than considering the multiple EoE studies that describe this disparity as repeated negative results, it may be that they instead support the existence of an alternative pathophysiology for the propagation of this Th2 disease. EoE as an autonomous Th2 disease relying exclusively on esophageal mucosal constituents would also explain why EoE by consensus definitions has always been restricted to the esophagus. The above studies are consistent with EoE, as well as other Th2 diseases, being able to employ localized release of TSLP to initiate the T2 inflammation cascade and the consequential tissue remodeling. The unique feature of EoE may ultimately be established that it employs this localized release of TSLP exclusively. Future work will be able to examine this hypothesis in a more direct fashion with *in vitro* models and with newer therapeutic approaches.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Search terms used in PubMed

Database	PubMed
Date	Initial search: 04/23/2020 Most recent update: 01/21/2022
Strategy	#1 AND #2 AND #3 *Table 1* and *2* #1 AND #4 *Table 3* and *4* (Eosinophilic esophagitis for *Tables 1* and *3*) (Asthma or atopic dermatitis or chronic rhinosinusitis for *Tables 2* and *4*)
#1	"Eosinophilic esophagitis" or "Asthma" or "Atopic dermatitis" or "Chronic rhinosinusitis"
#2	"Serum" or "Plasma" or "Blood"
#3	"Biomarkers" or "Interleukin-5" or "Interleukin-13" or "Eotaxin-3" or "Periostin" or "Thymic stromal lymphopoietin" or "IgG4" or "Eosinophil count" or "IgE" or "Eosinophil cationic protein" or "Eosinophil-derived neurotoxin" or "Thymus and activation-regulated chemokine" or "15(S)-HETE" or "Transforming growth factor β1" or "Major basic protein"
#4	"Biological therapy" or "Mepolizumab" or "Reslizumab" or "Omalizumab" or "QAX576" or "RPC4046" or "Dupilumab" or "Infliximab" or "Benralizumab" or "Tezepelumab" or "Tralokinumab" or "Lebrikizumab" or "Fezakinumab" or "Nemolizumab"

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