



Eosinophilic Esophagitis: Existing and Upcoming Therapies in an Age of Emerging Molecular and Personalized Medicine

Ian F. Slack¹ · Justin T. Schwartz¹ · Vincent A. Mukkada² · Shawna Hottinger¹ · J. Pablo Abonia¹

Published online: 6 June 2020

© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Purpose of Review Recent research efforts have spurred great progress in the diagnosis and management of eosinophilic esophagitis (EoE). Nonetheless, challenges remain in addressing disease burden and impairment in the growing EoE population. We highlight work from the Cincinnati Center for Eosinophilic Disorders, the Consortium of Eosinophilic Gastrointestinal Disease Researchers, and others that address these ongoing challenges.

Recent Findings New tools for characterizing EoE disease activity include the EoE Histology Scoring System (EoEHSS), endoscopic alternatives, validated patient-reported outcome (PRO) questionnaires, and investigational biomarkers. These diagnostic and monitoring strategies have been complemented by advances in EoE therapy. Treatment modalities have refined the traditional approaches of dietary elimination, swallowed steroids, and proton pump inhibitors (PPI), and biologics offer promise for future treatment.

Summary This review summarizes EoE advances in disease management and newly defined EoE endotypes that may serve as the foundation for EoE-personalized medicine.

Keywords Eosinophilic esophagitis · Diagnosis · Treatment · Endotype

Introduction

The year 2020 marks the 25th anniversary of Kevin Kelly and colleagues' publication of a cohort of children with esophageal eosinophilia responsive to dietary changes [1]. The paper sparked the idea of eosinophilic esophagitis (EoE) as a food-triggered condition and contributed to a subsequent flurry of research into its pathophysiology. Subsequent work by many groups ultimately yielded a consensus that defined EoE as a clinicohistologic diagnosis requiring both suggestive

esophageal symptoms and greater than or equal to 15 eosinophils per high-power field (HPF) on esophageal tissue biopsy. This is felt to be triggered by aberrant Th2 inflammation in response to environmental stimuli [2, 3]. Clinical investigation has revealed that symptoms poorly correlate to histologic disease activity, making ongoing monitoring and treatments difficult [4], and these challenges have been compounded by an increasing incidence/prevalence of EoE [5–7]. Furthermore, new research into EoE endotypes has documented significant diversity at the cellular and clinical level [8, 9]. Thus, the need for research into EoE mechanisms and treatment is greater than ever. In this review, we summarize the application of new research and therapeutic tools to EoE, including advanced technologies, biologic therapies, and personalized medicine (Fig. 1). We anticipate that these advances will lay the groundwork for further EoE discoveries.

This article is part of the Topical Collection on *Pediatric Allergy and Immunology*

✉ J. Pablo Abonia
Pablo.Abonia@cchmc.org

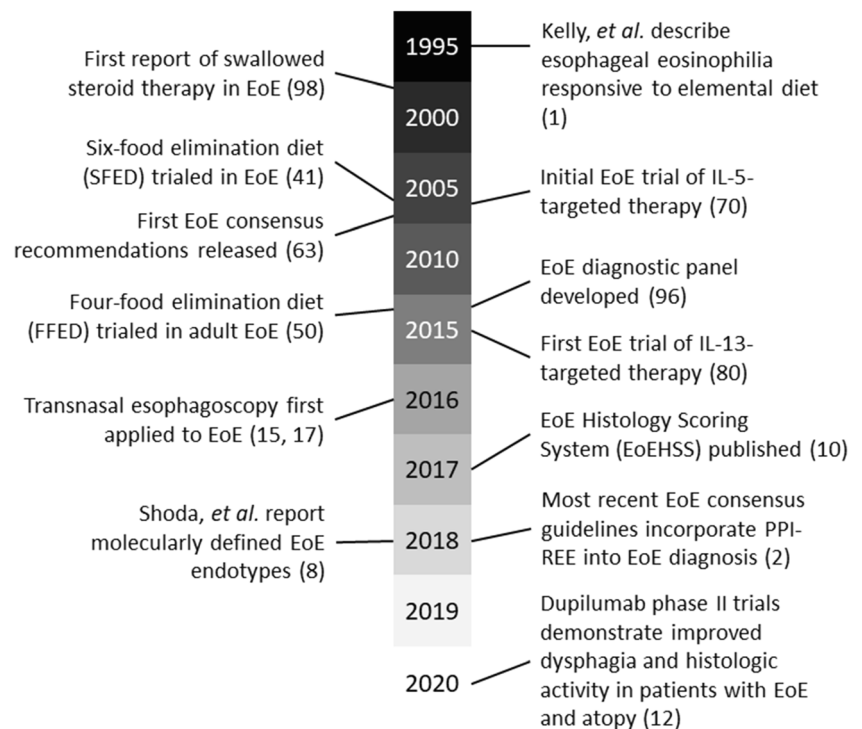
¹ Division of Allergy and Immunology, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7028, Cincinnati, OH 45229, USA

² Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Diagnosis and Monitoring

Eosinophilic esophagitis (EoE) requires a peak eosinophil count (PEC) of greater than or equal to 15 eosinophils per HPF in esophageal biopsy and exclusion of other sources of

Fig. 1 Evolution of EoE diagnosis and management over the past 25 years. EoE, eosinophilic esophagitis; anti-interleukin pathway antibodies; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia



tissue eosinophilia [2•]. PEC captures the degree of eosinophilic infiltration but fails to consider the extent of disease, as well as other histologic markers of EoE tissue injury. As research into EoE pathogenesis continues to identify a range of potential mechanisms of disease [8•, 9], additional histologic data and evaluation may provide important research and clinical data. The EoE Histology Scoring System (EoEHSS) was developed to address the spectrum of histologic differences observed in EoE [10] and provides a standardized method to assess the severity and extent of eight histologic features of EoE within esophageal biopsies. The EoEHSS was better able to distinguish treatment status than did PEC, and ongoing clinical trials utilize the EoEHSS for a multidimensional assessment of disease activity [8•, 11, 12•]. After the diagnosis of EoE has been made, recurrent endoscopy is currently required for monitoring of disease activity. However, the time, cost, and risks of anesthesia associated with endoscopy [13] have driven efforts to develop less invasive, surrogate measures for evaluating EoE activity and response to therapy.

Surrogate Measures for EoE Activity and Response to Therapy

Endoscopic Alternatives

Various alternatives to sedated esophagogastroduodenoscopy (EGD) have emerged for obtaining esophageal tissue samples, including transnasal esophagoscopy (TNE) and the

Cytosponge. TNE involves an unsedated, in-office procedure in which a gastroenterologist threads a small-caliber endoscope via the nares into the upper gastrointestinal tract [14]. The technique has been applied to both pediatric and adult EoE with similar biopsy quality to traditional endoscopic techniques [15–17]. Although TNE has been performed in patients as young as 3 years, the technique does require a degree of patient cooperation and has a reported failure rate of 2–3% in EoE across both pediatric and adult populations [16, 17].

The Cytosponge device offers an alternative method of esophageal sampling that avoids endoscopy entirely. A small, compressed sponge is ingested and expands in the stomach; the device is then retrieved from the stomach by an attached string [18]. On its ascent through the esophagus, the Cytosponge collects superficial specimens of esophageal mucosa that can then be processed and reviewed by standard pathologic techniques. Biopsy specimen sampling is random and cannot be targeted as in traditional endoscopic methods. The device has been trialed in adults with EoE and achieved a sensitivity of 75% and specificity of 86% for EoE histologic activity using the standard pathologic definition of greater than or equal to 15 eosinophils per HPF [19, 20]. Ongoing clinical trials are assessing the utility of the Cytosponge as a screening tool in EoE management [21].

Both TNE and the Cytosponge offer potential cost and time savings, as well as avoidance of anesthesia. However, they also present similar limitations as compared with traditional endoscopy, including the inability to perform esophageal dilations for stricture and the inability to be performed in young

children. As these endoscopic alternatives continue to transition from the research to the clinical realm, these techniques will likely supplement, rather than eliminate, traditional endoscopy.

Developing Noninvasive Biomarkers

In addition to investigating endoscopic alternatives, a significant body of research has focused on biomarkers as an option for noninvasive monitoring. A recent systematic review of minimally invasive biomarkers in EoE identified a rapid increase in biomarker research since 2014 while also identifying obstacles to EoE biomarker development [22]. Most notably, these tests must be specific to EoE rather than general atopy. Various approaches have been used, including measuring eosinophil products and surface markers, humoral immunity, and markers of mucosal damage. Discussions of these various approaches are beyond the scope of this review; however, we would like to highlight circulating blood eosinophil progenitor (EoP) cells and the esophageal string test as promising biomarker examples.

EoPs represent a rare population of eosinophil lineage-committed, CD34⁺ granulocyte progenitor cells that are mobilized into the peripheral blood during allergic inflammation [23, 24]. In children on dietary therapy, blood EoP levels have been shown to correlate with disease activity as assessed by peak eosinophil counts [25, 26], as well as correlate with the tissue pathologic changes quantified by the EoEHSS [27]. Notably, these differences were seen regardless of a history of other atopic conditions, including allergic rhinitis or atopic dermatitis. Likewise, inhaled, intranasal, or topical skin steroid therapy had no effect on serum EoP levels (patients with swallowed or systemic steroid exposure were excluded from recruitment). In contrast, antihistamine therapy was associated with a significant decrease in serum EoP levels, the mechanism of which remains unclear. When accounting for antihistamine therapy, the investigators were able to achieve 100% sensitivity and 77.8% specificity for serum EoP levels identifying active EoE disease. However, despite the promise of EoPs as a noninvasive biomarker, hurdles remain. The assay is technically challenging due to the rarity of this population in the blood. Additionally, EoP levels have not been studied yet in patients with EoE who are on swallowed steroid therapies. Ongoing research is working to improve testing accessibility and application to broad EoE populations.

The esophageal string test (EST) circumvents peripheral specimen collection to obtain biomarkers directly from the esophageal lumen [28]. The device attaches a gelatin capsule to a nylon string; the capsule is swallowed, and the filament is allowed to dwell in the esophagus, where it collects

eosinophil-associated proteins (EAP); these EAPs are then quantified and correlated to eosinophilic inflammation [29]. Earlier studies used prolonged dwell times for optimal sampling, but recent work analyzed the EST in patients with EoE with a brief dwell time of 1 h [30]. The 1-h EST obtained various EAPs that correlated well with PEC and endoscopic abnormalities identified on subsequent EGD. Current EST methods do have lower sensitivities and specificities than the gold-standard EGD biopsy; furthermore, 14% of patients in the recent EST study were unable to tolerate the device due to gagging. However, the EST offers an attractive vehicle for new EoE biomarkers that are otherwise difficult to isolate from blood or other specimens. Overall, the ideal biomarker—noninvasive, accessible, and accurate—remains elusive. Nonetheless, biomarkers combined with other tools, including patient-reported outcome (PRO) approaches and endoscopic alternatives, are poised to revolutionize current EoE monitoring techniques.

Evaluating Patient Symptoms

Recent work in EoE monitoring has also focused on alternatives to histologic examination of the esophagus. Patient symptoms have previously demonstrated poor correlation to disease activity [4]. However, work with PRO methodology endorsed by the FDA [31] has resulted in some validated tools for the evaluation of patient symptoms. The goal of these tools is to provide standardized and reproducible measures of patient symptoms, which could be applied toward therapeutic clinical trials and ongoing disease monitoring. The Eosinophilic Esophagitis symptom Activity Index (EEsAI) was developed and validated in adult patients for symptom recall over a 7-day period [32, 33]. Scores correlated with PEC and other endoscopic features of EoE, but the EEsAI scores alone were not sufficient to differentiate patients with active versus inactive disease. The pediatric PRO tools have undergone iterative development, with the Pediatric Eosinophilic Esophagitis Symptom Score, version 2 (PEESS v2.0), being the most recent EoE symptom PRO questionnaire [34, 35]. The PEESS v2.0 provides a 30-day recall self-report for patients as young as 5 years and parent proxy report for patients as young as 3 years, but it has yet to be fully validated. Much like the EEsAI in adults, the PEESS v2.0 offers correlation with architectural changes in EoE but cannot determine disease activity in isolation [34]. Despite these shortcomings, these PRO tools, along with quality of life metrics, such as the PedsQL-EoE [36], offer a means of collecting patient symptom and impairment data. These tools may eventually transition to clinical use for monitoring of disease control, much like the asthma control test (ACT) [37] that provides objective measures of asthma control.

Therapy

EoE was initially identified as a food-triggered condition in the mid-1990s with improvement in esophageal eosinophilia on an elemental diet [1]. Since that time, multiple EoE treatment strategies have been developed, each with advantages and drawbacks. We will discuss existing therapeutic options along with emerging treatment options.

Current Mainstays of Therapy

Dietary Therapies

Dietary management represented the initial EoE treatment strategy. Two primary methods have emerged: elemental diet and specific food elimination. Elemental diet therapy initially provides nutrition via amino acid–based formulas alone with no solid food intake and represents one of the most successful EoE therapies for control of symptoms and histologic disease activity, with meta-analysis suggesting 90% response rate [38]. The method contains several drawbacks, including the expense of formula and requiring a feeding tube in the majority of individuals on therapy [39]. Skin prick testing and patch testing were utilized in an effort to identify specific foods that could be excluded from a patient's diet and could achieve control of esophageal eosinophilia [40–44]. However, the utility of food allergy testing is currently questionable as the food patch tests in particular have not been standardized and IgE-specific testing has not demonstrated a significant additional benefit. These drawbacks in part spurred the development of the six-food elimination diet (SFED) for management of EoE [41]. This strategy requires the avoidance of cow's milk, soy, egg, wheat, peanut and tree nuts, and seafood based on rates of allergenicity and risk of esophageal injury. The approach offers a 72% histologic response rate in the pediatric and adult populations in meta-analysis (Arias et al., 2014). Furthermore, there was no clear advantage to using skin-prick/patch testing to guide dietary restrictions vs. using an empiric SFED [45, 46]. Thus, the utilization of these tests has declined except for the purpose of identifying patients at risk for anaphylaxis, which is observed in up to 27.1% of patients with EoE [47]. The SFED notably does allow solid food intake and imposes fewer social restrictions for the family when dining. Nonetheless, the restrictions also incur time and cost that can impair adherence and disease control [48]. Additionally, elemental diet and SFED therapies both require patients to undergo repeat endoscopic evaluation following any new food introduction to ensure no flaring of disease. Thus, newer strategies have been developed to minimize the impact of restriction and repeated endoscopies while optimizing the opportunity for clinical response. Four-food elimination diets (FFED) have been trialed in both children and adults with an approximate 10% decrease in histologic remission rate compared

with that of SFED [49, 50]. Of note, the two groups approached FFED differently. Molina-Infante et al. eliminated dairy (cow, sheep, and goat's milk), gluten-containing grains, legumes, and egg in adults with EoE and achieved a 54% remission rate; Kagalwalla et al.'s pediatric cohort avoided cow's milk, wheat, egg, and soy and achieved a 64% remission rate. Both studies commented on the decreased time required for food reintroduction and number of required endoscopies as benefits of the FFED approach. Although both Molina-Infante and Kagalwalla et al. studies contained relatively small study cohorts (52 and 72 patients, respectively), their approaches have spurred a paradigm shift in EoE dietary management. Their success suggested that less restrictive diets could achieve relatively similar clinical efficacy with decreased therapeutic burdens on patients and families. The tiered diet elimination strategy was investigated further with the 2-4-6 study [51]. This European trial recruited children and adults with EoE for food elimination management. Patients initially avoided two food groups (dairy and gluten-containing grains) and were evaluated for histologic remission. Non-responders were escalated to FFED (dairy, gluten-containing grains, legumes, and egg); patients who continued to demonstrate active disease on FFED were ultimately transitioned to SFED, thus adding avoidance of seafood and peanut/tree nut. Overall, the group achieved a 79% remission rate, with 43% of patients responding after two-food elimination. The trial suggests that a significant proportion of food elimination-responsive patients achieve histologic remission on less restrictive diets and that personalized dietary strategies may offer the greatest success. Ongoing research studies through the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) are further broadening dietary approaches with comparisons of single-food, four-food, and six-food elimination strategies and will help shape the future of EoE dietary therapy in pediatric and adult patients [52, 53].

Swallowed Steroids

Swallowed steroid therapies for EoE offer an alternative to diet-based interventions. The two most common approaches include either swallowed fluticasone from a metered-dose inhaler or budesonide nebulization solution mixed with a sugar substitute to form a slurry with both approaches intended to allow topical application to the esophagus. The American College of Gastroenterology recommends either as first-line pharmacologic therapy for EoE, with head-to-head comparisons demonstrating equivalent efficacy of either drug at inducing histologic remission [44, 54]. Despite consensus on agents, the optimal steroid dose for EoE remains in question. Histologic remission rates do increase with increasing steroid dosing; however, histologic improvements do not necessarily translate into improved clinical symptoms [55, 56]. The histologic benefits must also be weighed against the adverse

effects of daily swallowed steroids. Local steroid effects include oral and esophageal candidiasis, which has been reported to occur in up to 26% of patients on therapy, although this is in significant excess of what has been noted anecdotally by the authors [57]. Systemic effects are mitigated by the high level of first-pass metabolism of both fluticasone and budesonide [58, 59]. Nonetheless, a subset of patients on swallowed steroid therapies have evidence of an impaired adrenal axis, although the clinical significance of this finding is still uncertain [60, 61]. Currently, the American College of Gastroenterology provides a broad dosing recommendation to allow tailored therapy and optimization of risks and benefits of therapy [44].

Comparisons between food elimination and swallowed steroid therapies are difficult due to the heterogeneity of available studies. Meta-regression analyses suggest that the therapies are generally equivalent at inducing histologic remission, with response rates of roughly 70% [62]. Unfortunately, this leaves a significant population of patients with EoE with histologically active disease. This group of patients with unresolved disease activity expands further when considering real-world therapy limitations such as adherence or therapy-limiting side effects. Ongoing efforts are identifying promising therapies beyond diet or steroid strategies.

Proton Pump Inhibitors

In recent years, PPIs have become one of the first-line therapy options for EoE. Previous definitions of EoE required an empiric PPI trial prior to diagnosis [63, 64]. The PPI trial was intended to exclude gastroesophageal reflux disease (GERD) from the differential diagnosis of esophageal eosinophilia; patients whose condition improved on PPI therapy were classified as having PPI-responsive esophageal eosinophilia (PPI-REE). Further study into PPI-REE revealed that PPIs may improve esophageal eosinophilia independent from their impact on reflux [65]. Furthermore, clinical, endoscopic, and transcriptional analyses failed to identify clinically significant differences between EoE and PPI-REE [66, 67]. In an effort to streamline the esophageal eosinophilia workup, PPI-REE was integrated into the EoE diagnosis [2•]. The retooled EoE algorithm now not only allows the option of PPI therapy upon EoE diagnosis but also allows providers to pursue alternative therapies pending clinical scenario. Though high-dose PPI is used as either a primary or adjunctive therapy for EoE, it is not entirely without risk as there are concerns for potential side effects including possible increased risk for fracture [68].

Emerging Biologic Therapy

Eosinophil-Targeted Therapies

Interleukin 5 (IL-5)'s central role in eosinophil proliferation and survival [69] has made it an attractive target for EoE

therapy. Initial results from a small open-label phase I/II trial of mepolizumab, an anti-IL-5 agent, demonstrated encouraging results [70]. The study included 4 adults with chronic EoE whose disease activity persisted despite dietary modifications. Three of these four had a history of steroid therapy, either systemic or swallowed, but continued to demonstrate histologically active disease. All four patients demonstrated histologic remission along with improvements in endoscopic appearance and symptom report after 3 months of mepolizumab therapy. These early data suggested a role for mepolizumab in EoE therapy, but subsequent trials demonstrated a more modest effect of mepolizumab on disease activity. Larger studies using mepolizumab or reslizumab, an alternative anti-IL-5 agent, repeatedly demonstrated mitigated histologic disease activity but fell short of disease remission when applied to a broad EoE population [71–73]. Anti-IL-5 agents may have varying impact on subtypes (e.g., PPI-REE) and/or endotypes of EoE due to the condition's heterogeneity, and further investigation may identify whether there is a clinical role for mepolizumab or reslizumab in EoE going forward. Other eosinophil-targeted therapies, including benralizumab and anti-siglec-8 biologics, have direct cytotoxic effects on eosinophils that may have therapeutic advantages as compared with those which target the IL-5 cytokine [74, 75]. Investigation into these agents is ongoing and may provide future therapeutic possibilities [76, 77].

IL-13-Targeted Therapies

Interleukin 13 (IL-13) is another Th2 cytokine implicated in EoE pathogenesis. IL-13 overexpression in animal models generates eosinophilic esophageal inflammation [78], and IL-13 levels are elevated in the esophageal mucosa of patients with active EoE [79]. Initial IL-13-targeted therapies were first published in 2015 with QAX576, an anti-IL-13 monoclonal antibody [80]. Twenty-five adults with EoE were randomized to QAX576 or placebo with a primary endpoint of 75% reduction in PEC. Ultimately, only 40% of patients evidenced the target eosinophil reduction, though the study group's mean PEC decreased by 60% after therapy. This decrease in eosinophil load was maintained for a 6-month period following the final administration of study drug. The lasting effects of IL-13 blockade may be mediated in part through transcriptional regulation, as transcriptomic analysis of patients demonstrated normalized expression of several genes associated with EoE.

A larger randomized trial of IL-13 blockade was performed in adults with EoE using RPC4046, another monoclonal antibody targeting IL-13 [11]. Half of the 65 patients on study drug evidenced a decrease in PEC to < 15 eosinophils per HPF, and IL-13 blockade was associated with improved EoEHSS scores. After the 16-week initial trial, the study was converted to a year-long, open-label trial in which all patients were offered RPC4046 for 36 additional weeks

[81]. Sixty-six of the prior 90 patients participated in the open-label trial and demonstrated ongoing improvement in PEC and EoEHSS. Notably, patients' EoE disease activity had an equivalent response irrespective of whether they had a history of steroid-refractory disease, suggesting promise for IL-13 blockade in difficult-to-treat EoE.

Although several IL-13-targeting agents are under development, dupilumab is currently the only clinically available anti-IL-13 agent because of its FDA-approved indications for atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis [82–84]. The monoclonal antibody targets the IL-4 α receptor subunit, blocking the action of both IL-4 and IL-13. Given its effectiveness against a broad array of atopic disease, dupilumab offers an exciting prospect for EoE therapy, and clinical trial data were recently published [12•]. The phase II trial enrolled patients with comorbid EoE and atopy; given dupilumab's prior effectiveness with other atopic conditions, the investigators postulated that the presence of atopy could select for cases most responsive to the drug. Furthermore, the trial's primary outcome was targeted toward dysphagia symptoms, with histologic improvements included as secondary outcomes. Forty-seven adults were enrolled, with 23 patients receiving weekly dupilumab for a 12-week period. Over 20% of patients receiving dupilumab evidenced symptomatic remission, defined as an EEsAI score ≤ 20 , and dysphagia scores were significantly improved as compared with those of the placebo group. Furthermore, histologic changes were impressive, with a mean 93% decrease in PEC, and there were improvements in both severity (grade) and extent (stage) on the EoEHSS. Although the trial period was brief, dupilumab was well-tolerated, and there was no increase in peripheral eosinophilia, which had been noted in a prior dupilumab trial in asthma [85]. However, the effects of dupilumab on a broad EoE population, including children and individuals without atopic comorbidities, remain unknown.

Upcoming Therapies of Interest

Other EoE therapeutic targets are under active investigation, though clinical data are limited at this time. Vedolizumab is an anti- $\alpha 4\beta 7$ integrin monoclonal antibody that disrupts lymphocyte binding to MadCAM1 on intestinal endothelial cells; the drug is FDA approved for Crohn disease and ulcerative colitis [86]. Although MadCAM1 is not typically expressed in the esophageal endothelium, *in vitro* studies suggest that the molecule may be induced in the esophagus by inflammatory mediators [87]. Two case reports of patients with Crohn disease on vedolizumab noted improvement in the patients' concurrent EoE while on biologic therapy [88, 89]. A subsequent case series trialed vedolizumab in five patients with eosinophilic gastrointestinal disease (EGID) involving multiple sites of the GI tract [90]. Three of 5 patients began the study with esophageal involvement. The patients had a

variable response, with 2 of 5 reporting improvement in EGID symptoms with corresponding reduced tissue eosinophilia. However, one patient had an increase in esophageal eosinophilia on therapy, and two others declined post-therapy biopsies. The small cohort and lack of controls make it difficult to generalize about vedolizumab's utility in EoE. Given the potential context-dependent expression of MadCAM1 in the esophagus, vedolizumab's clinical effects in EoE may be most notable in the setting of other systemic inflammatory disorders, such as inflammatory bowel disease.

Aside from biologics, our group is interested in repurposing existing medications with activity against EoE. Given the association between EoE and connective tissue phenotypes [91], we are currently investigating losartan for use in patients with EoE [92]. Connective tissue disorders are a diverse group of genetic disorders that share disordered TGF- β signaling [93]. Angiotensin receptor blockers mitigate TGF- β signaling [94] and may offer therapeutic benefit to the EoE population. Results of these trials are forthcoming and could potentially offer an accessible adjunctive medicine.

EoE Endotypes: an Advance Toward Molecular and Personalized Medicine

The heterogeneity of EoE clinical presentation and response to existing therapies has led to speculation that distinct disease profiles exist within the condition [95]. Shoda et al. further delineated these endotypes using molecular, histologic, and endoscopic approaches [8•]. The group used the EoE diagnostic panel (EDP) [96], a transcriptional analysis of 94 genes associated with EoE, to subgroup a large cohort of pediatric and adult patients with EoE via cluster analysis. These subgroups were then correlated with EoEHSS findings, endoscopic observations, and clinical histories. The analysis identified three primary endotypes of roughly equal distribution across the cohort. EoE endotype 1 (EoEe1) was notable for normal-appearing mucosa and steroid-responsive disease. EoE endotype 2 (EoEe2) demonstrated elevated inflammatory signatures on the EDP and correlated with steroid-refractory disease. The final EoE endotype (EoEe3) corresponded to a fibrostenotic phenotype with narrow-caliber esophagus and decreased expression of epithelial-differentiation transcripts. Further clustering analysis focused on Th2 cytokine expression identified additional subgroups of patients with active EoE [9]. Th2-associated cytokine transcription was measured using a subset of EDP genes, with subgroups identified by unsupervised clustering. These groups were then organized from group I, with the lowest *IL5* expression, to group V, with the highest *IL5* expression. Although there was no significant difference in PEC among groups I–V, their underlying endotypes were quite distinct. Group I generally corresponded

to EoEe1, whereas group V displayed the inflammatory EoEe2. Groups II–IV largely demonstrated the fibrostenotic EoEe3, with groups III and IV showing elevated *IL13* transcription. It is not clear whether these endotypes and/or groups represent chronologic phases of disease progression, disparate pathologic mechanisms, or both. Regardless, these endotypes and their cytokine profiles offer an important perspective into EoE disease that is missed when evaluating by PEC alone. As discussed above, the Th2 cytokine family offers an attractive EoE therapeutic target, and these endotypes may direct personalized therapies for optimal EoE treatment.

Conclusion

Despite the growing appreciation of EoE, the condition remains a rare disease with an estimated incidence of 1/10,000 individuals per year [97]. Rare conditions offer particular challenges to researchers, as the logistic barriers of assembling and analyzing a patient cohort can prove massive. Specialized eosinophil care and research centers have developed across the country to address these specific challenges. The Cincinnati Center for Eosinophilic Disorders (CCED) is one such example of a regional eosinophil center. Work by the CCED and other national centers has been coordinated by the national CEGIR; together, the CCED and CEGIR have provided the framework for several of the EoE tools discussed in this review, including the EoEHSS, PEES v2.0, blood EoP levels, and the EDP. Many of these tools have been integrated in endotype analysis to provide an in-depth picture of each patient's individual EoE signature. By targeting traditional and biologic therapies to particular endotypes, we hope to achieve a new degree of EoE disease control. Furthermore, CEGIR's national presence has made large-scale clinical trials for treatment advances possible, paving a pathway to personalized medicine in EoE.

Compliance with Ethical Standards

Conflict of Interest Mrs. Hottinger reports grants from the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR; Administrative Core, U54AI117804), outside the submitted work. Dr. Mukkada reports consulting fees from Shire/Takeda, outside the submitted work. The other authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

- Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503–12.
- Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated International Consensus Diagnostic Criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022–33 e10 **Most recent EoE consensus guidelines, incorporating PPI-REE into EoE diagnosis.**
- Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol*. 2001;108(6):954–61.
- Pentiuk S, Putnam PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2009;48(2):152–60.
- DeBrosse CW, Collins MH, Buckmeier B, Greenburg A, Allen C, Abonia JP, et al., editors. The “epidemic” of eosinophilic esophagitis (ee) is due to increased recognition of a chronic disorder. *J Allergy Clin Immunol*; 2010.
- Fujiwara Y, Sugawa T, Tanaka F, Tatsuwaki H, Okuyama M, Hayakawa T, et al. A multicenter study on the prevalence of eosinophilic esophagitis and PPI-responsive esophageal eosinophilic infiltration. *Intern Med*. 2012;51(23):3235–9.
- Nantes Castillejo O, Zozaya JM, Jimenez-Perez FJ, Martinez-Penuela JM, Borda F. Incidence and characteristics of eosinophilic esophagitis in adults. *An Sist Sanit Navar*. 2009;32(2):227–34.
- Shoda T, Wen T, Aceves SS, Abonia JP, Atkins D, Bonis PA, et al. Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: a cross-sectional study. *Lancet Gastroenterol Hepatol*. 2018;3(7):477–88 **Identifies defined endotypes within EoE.**
- Dunn JL, Shoda T, Caldwell JM, Wen T, Aceves SS, Collins MH, et al. Esophageal type 2 cytokine expression heterogeneity in eosinophilic esophagitis in a multi-site cohort. *J Allergy Clin Immunol*. 2020.
- Collins MH, Martin LJ, Alexander ES, Boyd JT, Sheridan R, He H, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus*. 2017;30(3):1–8.
- Hirano I, Collins MH, Assouline-Dayana Y, Evans L, Gupta S, Schoepfer AM, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. *Gastroenterology*. 2019;156(3):592–603. e10.
- Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology*. 2020;158(1):111–22. e10 **Phase 2 results of dupilumab in EoE.**
- Zaccariello MJ, Frank RD, Lee M, Kirsch AC, Schroeder DR, Hanson AC, et al. Patterns of neuropsychological changes after general anaesthesia in young children: secondary analysis of the Mayo Anaesthesia Safety in Kids study. *Br J Anaesth*. 2019;122(5):671–81.

14. Postma GN, Cohen JT, Belafsky PC, Halum SL, Gupta SK, Bach KK, et al. Transnasal esophagoscopy: revisited (over 700 consecutive cases). *Laryngoscope*. 2005;115(2):321–3.
15. Friedlander JA, DeBoer EM, Soden JS, Furuta GT, Menard-Katcher CD, Atkins D, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. *Gastrointest Endosc*. 2016;83(2):299–306. e1.
16. Nguyen N, Lavery WJ, Capocelli KE, Smith C, DeBoer EM, Deterding R, et al. Transnasal endoscopy in unsedated children with eosinophilic esophagitis using virtual reality video goggles. *J Clin Gastroenterol Hepatol*. 2019;17(12):2455–62.
17. Philpott H, Nandurkar S, Royce SG, Gibson PR. Ultrathin unsedated transnasal gastroscopy in monitoring eosinophilic esophagitis. *J Gastroenterol Hepatol*. 2016;31(3):590–4.
18. Iqbal U, Siddique O, Ovalle A, Anwar H, Moss SF. Safety and efficacy of a minimally invasive cell sampling device (“Cytosponge”) in the diagnosis of esophageal pathology: a systematic review. *Eur J Gastroenterol Hepatol*. 2018;30(11):1261–9.
19. Katzka DA, Geno DM, Ravi A, Smyrk TC, Lao-Sirieix P, Miramedi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2015;13(1):77–83. e2.
20. Katzka DA, Smyrk TC, Alexander JA, Geno DM, Beitia RA, Chang AO, et al. Accuracy and safety of the cytosponge for assessing histologic activity in eosinophilic esophagitis: a two-center study. *Am J Gastroenterol*. 2017;112(10):1538–44.
21. Mayo Clinic. Cytosponge and dietary therapy in EoE. <https://ClinicalTrials.gov/show/NCT02599558>; 2015.
22. Hines BT, Rank MA, Wright BL, Marks LA, Hagan JB, Straumann A, et al. Minimally invasive biomarker studies in eosinophilic esophagitis: a systematic review. *Ann Allergy Asthma Immunol*. 2018;121(2):218–28.
23. Mori Y, Iwasaki H, Kohno K, Yoshimoto G, Kikushige Y, Okeda A, et al. Identification of the human eosinophil lineage-committed progenitor: revision of phenotypic definition of the human common myeloid progenitor. *J Exp Med*. 2009;206(1):183–93.
24. Sehmi R, Smith S, Kjarsgaard M, Radford K, Boulet LP, Lemiere C, et al. Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. *J Clin Exp Allergy*. 2016;46(6):793–802.
25. Morris DW, Stucke EM, Martin LJ, Abonia JP, Mukkada VA, Putnam PE, et al. Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2016;138(3):915–8 e5.
26. Henderson A, Magier A, Schwartz JT, Martin LJ, Collins MH, Putnam PE, et al. Monitoring eosinophilic esophagitis disease activity with blood eosinophil progenitor levels. *J Pediatr Gastroenterol Nutr*. 2020;70(4):482–8.
27. Schwartz JT, Morris DW, Collins MH, Rothenberg ME, Fulkerson PC. Eosinophil progenitor levels correlate with tissue pathology in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2019;143(3):1221–4. e3.
28. Thomas G, Goldsmid J, Wicks A. Use of the Enterotest duodenal capsule in the diagnosis of giardiasis. *S Afr Med J*. 1973;47(11):2219–20.
29. Furuta GT, Kagalwalla AF, Lee JJ, Alumkal P, Maybruck BT, Fillon S, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut*. 2013;62(10):1395–405.
30. Ackerman SJ, Kagalwalla AF, Hirano I, Gonsalves N, Katcher PM, Gupta S, et al. One-hour esophageal string test: a nonendoscopic minimally invasive test that accurately detects disease activity in eosinophilic esophagitis. *Am J Gastroenterol*. 2019;114(10):1614–25.
31. Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health*. 2007;10:S125–S37.
32. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014;147(6):1255–66. e21.
33. Schoepfer A, Safroneeva E. Activity assessment of eosinophilic esophagitis. *Dig Dis*. 2014;32(1–2):98–101.
34. Aceves SS, King E, Collins MH, Yang GY, Capocelli KE, Abonia JP, et al. Alignment of parent- and child-reported outcomes and histology in eosinophilic esophagitis across multiple CEGIR sites. *J Allergy Clin Immunol*. 2018;142(1):130–8 e1.
35. Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. *BMC Gastroenterol*. 2011;11:126.
36. Franciosi JP, Hommel KA, Bendo CB, King EC, Collins MH, Eby MD, et al. PedsQL eosinophilic esophagitis module: feasibility, reliability, and validity. *J Pediatr Gastroenterol Nutr*. 2013;57(1):57–66.
37. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65.
38. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146(7):1639–48.
39. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98(4):777–82.
40. Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. *Gastroenterol Clin North Am*. 2007;36(1):75–91 vi.
41. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4(9):1097–102.
42. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130(2):461–7 e5.
43. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol*. 2013;131(3):797–804.
44. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol*. 2013;108(5):679–92.
45. Henderson CJ, Collins MH, Abonia JP, Putnam PE, Rothenberg ME. Reply: To PMID 22541246. *J Allergy Clin Immunol*. 2013;131(1):243–4.
46. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;129(6):1570–8.
47. Chehade M, Jones SM, Pesek RD, Burks AW, Vickery BP, Wood RA, et al. Phenotypic characterization of eosinophilic esophagitis in a large multicenter patient population from the consortium for food allergy research. *J Allergy Clin Immunol Pract*. 2018;6(5):1534–44 e5.
48. Wolf WA, Huang KZ, Durban R, Iqbal ZJ, Robey BS, Khalid FJ, et al. The six-food elimination diet for eosinophilic esophagitis

- increases grocery shopping cost and complexity. *Dysphagia*. 2016;31(6):765–70.
49. Kagalwalla AF, Wechsler JB, Amsden K, Schwartz S, Makhija M, Olive A, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15(11):1698–707. e7.
 50. Molina-Infante J, Arias A, Barrio J, Rodriguez-Sanchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. *J Allergy Clin Immunol*. 2014;134:1093–1099.e1.
 51. Molina-Infante J, Arias A, Alcedo J, Garcia-Romero R, Casabona-Frances S, Prieto-Garcia A, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. *J Allergy Clin Immunol*. 2018;141(4):1365–72.
 52. Cincinnati Children's Hospital Medical Center, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, Office of Rare Diseases, National Center for Advancing Translational Science. SOFEED: Six Food vs. One Food Eosinophilic Esophagitis Diet Study. <https://ClinicalTrials.gov/show/NCT02778867>; 2016.
 53. Cincinnati Children's Hospital Medical Center, Patient-Centered Outcomes Research Institute. Eosinophilic esophagitis intervention trial-1 food vs. 4 food elimination diet followed by swallowed glucocorticoids. <https://ClinicalTrials.gov/show/NCT02610816>; 2016.
 54. Dellon ES, Woosley JT, Arrington A, McGee SJ, Covington J, Moist SE, et al. Efficacy of budesonide vs fluticasone for initial treatment of eosinophilic esophagitis in a randomized controlled trial. *Gastroenterology*. 2019;157(1):65–73. e5.
 55. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2015;13(1):66–76. e3.
 56. Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in eosinophilic esophagitis: systematic review and meta-analysis of placebo-controlled randomized clinical trials. *J Gastroenterol Hepatol*. 2016;31(6):1111–9.
 57. Alexander JA, Jung KW, Arora AS, Enders F, Katzka DA, Kephart GM, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2012;10(7):742–9. e1.
 58. Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis*. 1982;122:86–95.
 59. Harding S. The human pharmacology of fluticasone propionate. *Respir Med*. 1990;84:25–9.
 60. Golekoh MC, Hornung LN, Mukkada VA, Khoury JC, Putnam PE, Backeljauw PF. Adrenal insufficiency after chronic swallowed glucocorticoid therapy for eosinophilic esophagitis. *J Pediatr*. 2016;170:240–5.
 61. Hsu S, Wood C, Pan Z, Rahat H, Zeitler P, Fleischer D, et al. Adrenal insufficiency in pediatric eosinophilic esophagitis patients treated with swallowed topical steroids. *Pediatr Allergy Immunol Pulmonol*. 2017;30(3):135–40.
 62. Cotton CC, Eluri S, Wolf WA, Dellon ES. Six-food elimination diet and topical steroids are effective for eosinophilic esophagitis: a meta-regression. *Dig Dis Sci*. 2017;62(9):2408–20.
 63. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133(4):1342–63.
 64. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3–20 e6 quiz 1-2.
 65. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102(6):1301–6.
 66. Dellon ES, Speck O, Woodward K, Gebhart JH, Madanick RD, Levinson S, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am J Gastroenterol*. 2013;108(12):1854–60.
 67. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol*. 2015;135(1):187–97. e4.
 68. Wang L, Li M, Cao Y, Han Z, Wang X, Atkinson EJ, et al. Proton pump inhibitors and the risk for fracture at specific sites: data mining of the FDA adverse event reporting system. *Sci Rep*. 2017;7(1):5527.
 69. Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood*. 1992;79(12):3101–9.
 70. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006;118(6):1312–9.
 71. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut*. 2010;59(01):21–30.
 72. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology*. 2011;141(5):1593–604.
 73. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129(2):456–63 e1–3.
 74. Ghazi A, Trikha A, Calhoun WJ. Benralizumab—a humanized mAb to IL-5R α with enhanced antibody-dependent cell-mediated cytotoxicity—a novel approach for the treatment of asthma. *Expert Opin Biol Ther*. 2012;12(1):113–8.
 75. Nutku E, Aizawa H, Hudson SA, Bochner BS. Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis. *Blood*. 2003;101(12):5014–20.
 76. Cincinnati Children's Hospital Medical Center, AstraZeneca. Benralizumab for Eosinophilic Gastritis. <https://ClinicalTrials.gov/show/NCT03473977>; 2018.
 77. Allakos Inc. A study of antolimumab (AK002) in patients with active eosinophilic esophagitis. <https://ClinicalTrials.gov/show/NCT04322708>; 2020.
 78. Zuo L, Fulkerson PC, Finkelman FD, Mingler M, Fischetti CA, Blanchard C, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R α 2-inhibited pathway. *J Immunol*. 2010;185(1):660–9.
 79. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol*. 2007;120(6):1292–300.
 80. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2015;135(2):500–7.
 81. Dellon ES, Collins MH, Rothenberg ME, Assouline-Dayana Y, Evans L, Gupta S, et al. Long-term efficacy and tolerability of RPC4046 in an open-label extension trial of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2020.
 82. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455–66.

83. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–48.
84. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315(5):469–79.
85. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–96.
86. Vermeire S, Loftus EV, Colombel J-F, Feagan BG, Sandborn WJ, Sands BE, et al. Long-term efficacy of vedolizumab for Crohn's disease. *Journal of Crohn's Colitis*. 2017;11(4):412–24.
87. Rafiee P, Ogawa H, Heidemann J, Li MS, Aslam M, Lamirand TH, et al. Isolation and characterization of human esophageal microvascular endothelial cells: mechanisms of inflammatory activation. *Am J Physiol Gastrointest Liver Physiol*. 2003;285(6):G1277–G92.
88. Nhu QM, Chiao H, Moawad FJ, Bao F, Konijeti GG. The anti- $\alpha 4\beta 7$ integrin therapeutic antibody for inflammatory bowel disease, vedolizumab, ameliorates Eosinophilic esophagitis: a novel clinical observation. *Am J Gastroenterol*. 2018;113:1261–3.
89. Taft TH, Mutlu EA. The potential role of vedolizumab in concomitant eosinophilic esophagitis and Crohn's disease. *Clin Gastroenterol Hepatol*. 2018;16(11):1840–1.
90. Kim HP, Reed CC, Herfarth HH, Dellon ES. Vedolizumab treatment may reduce steroid burden and improve histology in patients with eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol*. 2018;16(12):1992–4.
91. Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol*. 2013;132(2):378–86.
92. Cincinnati Children's Hospital Medical Center, Diabetes NIO, Digestive, Diseases K, Allergy NIO, Diseases I, et al. An open-label trial of losartan potassium in participants with eosinophilic esophagitis (EoE). <https://ClinicalTrials.gov/show/NCT03029091>; 2017.
93. Meester JA, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. *Ann Cardiothorac Surg*. 2017;6(6):582–94.
94. Ruiz-Ortega M, Rodríguez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. TGF- β signaling in vascular fibrosis. *Cardiovasc Res*. 2007;74(2):196–206.
95. Ferguson AE, Mukkada VA, Fulkerson PC. Pediatric eosinophilic esophagitis endotypes: are we closer to predicting treatment response? *Clin Rev Allergy Immunol*. 2017.
96. Wen T, Stucke EM, Grotjan TM, Kemme KA, Abonia JP, Putnam PE, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology*. 2013;145(6):1289–99.
97. Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin*. 2014;43(2):201–18.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.