

Accepted Manuscript

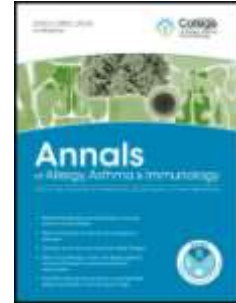
Title: Medical and dietary management of eosinophilic esophagitis

Author: Quan M. Nhu, Seema S. Aceves

PII: S1081-1206(18)30372-7
DOI: <https://doi.org/10.1016/j.anai.2018.05.006>
Reference: ANAI 2549

To appear in: *Annals of Allergy, Asthma & Immunology*

Received date: 12-3-2018
Revised date: 30-4-2018
Accepted date: 8-5-2018



Please cite this article as: Quan M. Nhu, Seema S. Aceves, Medical and dietary management of eosinophilic esophagitis, *Annals of Allergy, Asthma & Immunology* (2018), <https://doi.org/10.1016/j.anai.2018.05.006>.

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Medical and Dietary Management of Eosinophilic Esophagitis

Quan M. Nhu, M.D., Ph.D.^{1,2,3,*} and Seema S. Aceves, M.D., Ph.D.^{3,4,*}

¹Scripps Translational Science Institute, The Scripps Research Institute, La Jolla, CA, USA;

²Division of Gastroenterology & Hepatology, Department of Medicine, Scripps Clinic – Scripps

Green Hospital, CA, USA; ³Division of Allergy & Immunology, Departments of Pediatrics and

Medicine, University of California, San Diego, La Jolla, CA, USA; ⁴Rady Children's Hospital,

San Diego, San Diego, CA, USA

*Correspondence:

Dr. Quan Nhu (nhu.quan@scrippshealth.org; qnhu@ucsd.edu)

Dr. Seema Aceves (saceves@ucsd.edu)

Conflict of Interest: None

Funding: NIH/NCATS CTSA 5 UL1 TR001114, 5KL2 TR001112, and a Scripps Clinic Medical Group Research & Education Award (to Q.M.N.), and NIH/NIAID AI 092135 and AI 135034 (to S.S.A).

Keywords: Eosinophilic esophagitis, EoE, PPI-responsive esophageal eosinophilia, PPI-REE, treatment, management, corticosteroid, elimination diet therapy, biologic therapy, immunotherapy

Abbreviations: EoE, eosinophilic esophagitis; hpf, high power field; PPI, proton-pump inhibitor; PPI-REE, PPI-responsive esophageal eosinophilia; TFED, two-food elimination diet; FFED, four-food elimination diet; SFED, six-food elimination diet

Word Count: 3405

Figures: None

Tables: None

Key Messages

- Eosinophilic esophagitis is a chronic disease that can be treated with elimination diet or topical corticosteroids
- Biologic therapies for EoE are emerging
- Complications of EoE include strictures and food impactions that are due to tissue remodeling
- Successful therapy of EoE histology can reverse remodeling in a subset of patients

Abstract: Objective: Eosinophilic esophagitis (EoE) is a disease of chronic, allergen-driven, T-helper 2 (Th2) immune-mediated inflammation that progresses to fibrostenosis of the esophagus if left untreated. There are currently no FDA-approved drugs for the treatment of EoE. This review focuses on medical and dietary management of EoE.

Data Sources: Manuscripts on EoE treatments are identified on PubMed.

Study Selections: Original research, randomized control trials, retrospective studies, meta-analyses, case series, and on occasions, case reports of high relevance, are selected and reviewed.

Results: Current treatment strategies available to EoE patients center on monotherapy or combination therapy with dietary modification to exclude antigenic stimulation and topical corticosteroids to control Th2-mediated tissue inflammation and pathologic remodeling. Dilation as a rescue therapy for the narrowed, fibrostenotic, symptomatic esophagus can potentially be avoided with optimal medical and elimination diet therapies. The molecular mechanisms underlying EoE pathogenesis are being unraveled, from which targeted therapies can be developed and evaluated in pre-clinical and clinical studies. Current clinical research efforts focus on optimization of topical corticosteroid delivery, dosing, frequency, and duration of treatment, either alone or in combination with tailored elimination diet. Preliminary clinical trials with biologics targeting IL-5 and IL-13/IL-4 have been completed.

Conclusions: Topical corticosteroid, elimination diet, and dilation are the current treatment modalities for confirmed EoE. The use of proton-pump inhibitors (PPI) is being suggested as a potential regimen to treat EoE, based on evolving understanding of PPI-responsive esophageal eosinophilia (PPI-REE). The complexity of EoE treatment regimens and frequent follow ups require a multimodal, multi-disciplinary management approach to optimize patient care.

INTRODUCTION

Eosinophilic esophagitis (EoE) is an emerging chronic, allergen-driven, IL-13-dependent, T-helper 2 (Th2) immune-mediated inflammatory disease of the esophagus that almost uniformly progresses to fibrostenotic disease when untreated, resulting in tissue rigidity, reduced distensibility, and dysmotility.^{1, 2} Sub-optimally controlled, persistent inflammation underlies a natural progression to stricture formation, contributing to dysphagia and food impactions. EoE is defined as a marked esophageal eosinophilic inflammation (≥ 15 eosinophils per high power field (hpf)), with recruitment of other inflammatory cells including mast cells, lymphocytes,

basophils, and innate lymphoid cells.³ In children, EoE often presents clinically with abdominal pain, nausea, vomiting, regurgitation, feeding difficulty, and failure to thrive. Adults often present with dysphagia and food impactions, thought related to progression of esophageal motility dysfunction and fibrosis. Failure to thrive in children and lower body mass index in adults correlate with EoE severity, likely related to chronic nutritional deficit secondary to feeding difficulty, food aversion, recurrent dysphagia, and food impaction.^{4, 5} EoE creates a significant healthcare burden and an impaired quality of life.

A multimodal, multi-disciplinary management approach is often required and includes chronic corticosteroid treatment, proton-pump inhibitors (PPI), dietary antigen restriction, lifestyle modification, and repeated endoscopic diagnostic and therapeutic evaluations.⁶ There are currently no FDA-approved drugs for the treatment of EoE. Current efforts focus on controlling inflammation and tissue remodeling with medical therapy such as corticosteroids and investigational biologic agents, and on the exclusion of antigenic stimulation via elimination diet. The narrowed, fibrostenotic esophagus can be rescued by endoscopic intervention with dilation. Controlling inflammation has been suggested to decrease the need for subsequent esophageal dilation in adult EoE patients.⁷ Therefore, the focus of this review centers on medical and elimination diet therapies.

Topical Corticosteroids

Swallowed topical corticosteroids are a mainstay of treatment for pediatric and adult EoE patients. Current mainstays of topical esophageal deposition are not FDA approved and remain as puffed and swallowed steroids such as fluticasone or viscous preparations of budesonide.^{8, 9} In Europe, an effervescent budesonide tablet has also been used successfully in clinical trials.¹⁰ Topical fluticasone down-regulates eotaxin-3 mRNA expression and decreases esophageal

infiltration with eosinophils, mast cells, and lymphocytes.¹¹ Swallowed fluticasone reduces mRNA expression of IL-13 and reverses 98% of IL-13-induced EoE transcriptome to expression levels observed in healthy controls.¹² Topical fluticasone also partially, and at times completely, improves esophageal mucosal barrier integrity in EoE patients, with variable improvement of expression of barrier function-related genes, desmoglein-1, filaggrin, and E-cadherin.^{13, 14} Topical corticosteroid can modulate esophageal endoscopic and histologic remodeling, as supported by improvement of EoE-associated esophageal diameter, esophageal distensibility, and in the rates of food impaction.¹⁵ Treatment with topical corticosteroids in children decreases epithelial remodeling and fibrosis, and reduces subepithelial TGF- β 1 and nuclear Smad2/3-positive cells.^{3, 16} Peripheral blood eosinophils derived from topical corticosteroid-treated adult EoE patients maintain an activated phenotype; however, they express decreased surface CD18, resulting in diminished eosinophil adherence to ICAM-1, ICAM-2, and endothelial cells.¹⁷ This observation is in congruence with the recent finding that the migration of peripheral eosinophils to the esophagus and their survival *in situ* are linked to the upregulation and conformational change of α M β 2, also known as CD11b/CD18, integrin and its interaction with periostin, which is also highly expressed in EoE.^{18, 19} Treatment with budesonide for 12 weeks, or as short as 15 days, has been shown to achieve histologic, endoscopic, and clinical improvement in adolescent to adult EoE patients.^{20, 21} Budesonide treatment in adult EoE patients reduces esophageal eosinophil density, absolute peripheral eosinophilia, and serum levels of CCL17, CCL18, CCL26, eosinophil-cationic protein and mast cell tryptase.²²

Several studies have evaluated dosing, frequency, and length of treatment of topical corticosteroid therapy in EoE. High-dose fluticasone at 880 μ g twice daily for 3 months induces histologic remission in 65% to 77% of pediatric EoE patients.⁹ Responders are able to have

fluticasone dose reduced by 50%, which has been shown to remain effective in 73% to 93% of fluticasone-sensitive patients. In adults, it has been proposed to initiate induction corticosteroid therapy with 1 mg twice daily of budesonide until clinical response, which usually takes 2 to 4 weeks, followed by maintenance therapy with 0.25 mg twice daily of the same medication that can then be rescued with 1 mg twice daily dosing for 7 to 15 days during EoE flares.²³ Using this treatment strategy, deep remission – a combination of clinical symptom improvement; endoscopic inflammatory remission with complete absence of white exudates, furrows, and edema; and histological inflammatory remission with peak eosinophil count <5 eosinophils/hpf – is achieved at 89 weeks in 9.4% of adult EoE patients. Discontinuation of corticosteroid is recommended if patient maintains ≥ 6 months of deep remission. In this adult EoE cohort, corticosteroid discontinuation occurs at 104.7 weeks, with 81.8% experiencing EoE clinical relapse after a median of 22.4 weeks. It is possible that deep remission would have been more effectively achieved if a higher dose of budesonide was utilized for maintenance therapy. In another study, reducing the frequency of budesonide maintenance dosing to every other day in adults was not effective.²⁴ Together, these data suggest that a higher dose, daily budesonide or topical corticosteroid dose is necessary to potentially achieve complete histologic and endoscopic remission.

Efficacy of topical corticosteroids depends on the physical delivery of the drug to the esophageal mucosa, the mucosal retention rate, and the mucosal contact time.²⁵ Swallowing aerosolized corticosteroid has been shown to have variable delivery; whereas, oral viscous corticosteroid preparation can achieve superior esophageal mucosal delivery, resulting in improved treatment efficacy.^{25, 26} Proprietary and non-proprietary corticosteroid formulations that improve bioavailability and treatment efficacy are emerging, and should increase treatment

options for the clinicians and patients.^{10, 25, 27} Treatment of EoE patients with current corticosteroid formulations has been effective; however, a significant proportion of patients do not respond optimally or long term to medication therapy.²⁷ In a group of 32 EoE children on corticosteroids, followed over a mean of 5 years and a maximum of 10 years, patients who responded well to therapy had less esophageal fibrosis and improved endoscopic features, compared to those who responded sub-optimally.²⁸ Similarly, the adult fibrostenotic esophagus is often resistant to topical corticosteroids.^{3, 6} Mechanical and physical alterations in the fibrostenotic and dysmotile esophagus might affect the responsiveness of the structural and inflammatory cells to medical therapy.³ Rigid matrix can alter the contractility of esophageal fibroblasts and also modify their responsiveness to TGF- β 1.²⁹ Matrix stiffness can also modulate esophageal smooth muscle cells toward hypertrophy with increased collagen deposition.³⁰ In the fibrostenotic esophagus, topical corticosteroids might have decreased bioavailability *in situ*, potentially related to decreased penetration to the deeper esophageal layers where inflammation, fibrosis, and esophageal remodeling occur. Losartan – an angiotensin II receptor blocker approved for use in hypertension and heart failure – also suppresses active TGF- β 1 levels and inhibits collagen synthesis. Losartan is currently being explored in a clinical trial as a potential anti-fibrotic agent for EoE. Dual therapy with anti-fibrotic agents, such as losartan, and corticosteroids might synergistically target both inflammation-dependent and inflammation-independent, rigidity-dependent pathways in EoE and beyond.

Systemic administration of corticosteroids, although effective in EoE, are often less preferred due to undesired side effects. Topical corticosteroids are well tolerated, effective and safe,¹⁶ however, patients should avoid eating or drinking within 30 minutes of drug administration to maximize esophageal mucosal contact and retention. However, a number of

side effects from topical corticosteroids have been reported, including local infections and potential adrenal suppression. Asymptomatic esophageal candidiasis and herpes esophagitis have been reported with swallowed topical corticosteroid and resolved with antifungal and antiviral therapies, respectively.^{16, 31} In clinical trials, asymptomatic esophageal candidiasis occurred in approximately 20% (0% - 26%) of EoE patients treated with topical steroids.³² Sera from corticosteroid-treated EoE patients have higher specific IgE to *Candida albicans* than sera from corticosteroid-naïve EoE patients or controls.¹⁴ Adrenal insufficiency of unclear clinical significance has been observed in children on high-dose swallowed topical fluticasone propionate or oral viscous budesonide.^{33, 34}

Proton-pump inhibitor (PPI) therapy for EoE

High-dose PPI therapy is emerging as a potential first-line treatment for EoE rather than as a diagnostic strategy, based on our evolving understanding of PPI-responsive esophageal eosinophilia (PPI-REE) being in the EoE continuum.³⁵⁻³⁷ PPI monotherapy in children with esophageal eosinophilia decreased eotaxin-3 expression in the proximal esophagus.³⁸ A recent meta-analysis of 33 studies, comprising 619 patients with symptomatic esophageal eosinophilia, demonstrated that PPI therapy induced clinical response and histologic remission in 60.8% and 50.5% of patients, respectively.³⁹ Treatment with PPI *in vitro* inhibited Th2 cytokine-induced eotaxin-3 expression by interfering with promoter binding of signal transducer and activator of transcription 6 (STAT6) in EoE-derived esophageal epithelial cells.^{40, 41} Thus, treatment with PPI may, in part, dampen cellular responsiveness to Th2 cytokines and modulate esophageal eosinophilic infiltration, resulting in therapeutic benefits in EoE and PPI-REE via mechanisms that appear to be independent of acid suppression. On PPI maintenance, sustained remission has been observed in 73-86% of pediatric and adult PPI-REE patients, but this follow up is relatively

short and needs to be better determined.⁴² In addition, the side effects of chronic PPI use and the subset of subjects who respond and maintain response require further evaluation.⁴³⁻⁴⁶

Elimination diets in EoE

Dietary modification to remove allergen-derived antigenic stimulation has been shown to achieve EoE histologic and clinical remission and, sometimes in children, reversal of subepithelial fibrosis.⁴⁷⁻⁴⁹ Elemental diet is effective in improving symptoms and inducing histologic remission in pediatric EoE, with recurrence of symptoms upon open food challenges.⁵⁰ In pediatric and adolescent EoE patients, after an average of 8.5 days, elemental diet improves vomiting, abdominal pain and dysphagia, with concomitant histologic resolution.⁵¹ Elemental diet in one study improved esophageal inflammation in 88% of pediatric EoE patients, whereas six-food-elimination diet (SFED) excluding cow milk, wheat, egg, soy, peanut and seafood has been shown in another study to achieve histologic remission in 74% of patients.⁵² A four-food elimination diet (FFED) excluding only milk, wheat, egg, and soy in pediatric EoE patients for 8 weeks results in histologic remission in 64% of patients.⁵³ Clinical symptoms and endoscopic features are also improved. Allergy testing-directed elimination diet therapy by skin prick and atopy patch tests can be effective in guiding specific food exclusion in pediatric EoE, however its role in the evaluation of adult EoE patients has been questioned.⁵⁴⁻⁵⁶ A comparison of elemental diet, SFED, and allergy testing-directed elimination diet in a cohort of pediatric EoE patients has demonstrated remission rates of 96%, 81% and 65%, respectively.⁵⁷ A meta-analysis of 33 studies on 1128 children and 189 adult EoE patients shows that elemental diets are effective for 90.8% of cases, SFED for 72.1%, and allergy testing-directed elimination diet for 45.5% of cases.⁴⁹

The effect of elimination diet on inflammation and mucosal barrier integrity in adult EoE has been demonstrated. The effect on EoE remodeling in adults remains not as clear, although an improvement in esophageal distensibility has been recently demonstrated.¹⁵ In adult EoE patients, four weeks of elemental diet improves clinical symptoms in 88%, with complete histologic response in 71% of patients.⁵⁸ Endoscopic features and inflammation are also improved, with a significant reduction in gene expression of IL-13, IL-5, and TSLP on esophageal biopsies. Esophageal mucosal barrier integrity is also improved after elemental diet, with restoration of gene expression of filaggrin and desmoglein-1.⁵⁹ In a retrospective analysis, dietary elimination with SFED therapy or with targeted elimination diet achieved histologic remission in 56% and 32% of adult EoE patients, respectively.⁶⁰ The targeted elimination diet strategy excludes problematic food groups identified by the patient and by allergy testing; whereas, allergy testing-selective elimination diet excludes food groups identified by skin prick tests, and atopy patch tests. However, allergy testing-directed selective elimination diet has been shown to have suboptimal efficacy in adult EoE,⁶¹ and thus is generally not recommended. Histologic remission was achieved in 73.1% of adult EoE patients who underwent a rigorous six-week course of empiric SFED therapy excluding cereals, wheat, rice and corn; milk and dairy products; eggs; fish and seafood; legumes and peanuts; and soy; with extension to processed foods containing any of the six foods as ingredients.⁶² SFED therapy in adult EoE patients improves symptom score, reduces peak esophageal eosinophil count, and also reduces mast cell density and gene expression of mast cell chemotactic chemokines and mast cell proteases.⁶³ Four-food elimination diet excluding dairy products, wheat, egg, and legumes for six weeks demonstrates histologic remission in 54% of adult EoE patients.⁶⁴ Of the FFED-non-responders who proceeded to rescue SFED therapy additionally excluding fish/seafood and all nuts, 31%

achieved histologic remission. The FFED with rescue SFED strategy has a combined efficacy of 72%, suggesting that step-up augmentation of elimination diet could be a viable strategy. In a large prospective multicenter clinical trial, a 2-4-6 step-up elimination diet protocol in both pediatric and adult EoE patients was effective in both achieving clinicohistologic response and in identifying food triggers early, and thus avoided unnecessary dietary restriction.⁶⁵ In this protocol, patients were started on a 2-food elimination diet (TFED) excluding milk and gluten-containing cereals for 6 weeks. Non-responders were stepped up sequentially to elimination diet FFED initially, with the additional exclusion of egg and legumes; and ultimately to SFED, with the exclusion of nuts and fish/seafood. Each additional tier spanned a 6-week time frame. Overall, EoE remission was achieved in 43% of the TFED group, in 60% of patients receiving both TFED and FFED, and in 79% of patients receiving all three tiers of elimination diet therapy. Patients who failed any elimination diet therapy were rescued with 8 weeks of swallowed topical steroids – viscous oral budesonide 2 mg twice daily in adults and 1 mg twice daily in children, or swallowed fluticasone 800 µg twice daily. Histologic remission occurred in 79% of patients who underwent corticosteroid rescue therapy following a failed step-up antigen elimination protocol.⁶⁵

Food re-introduction has identified EoE triggers that include milk and dairy products, wheat/gluten, eggs, soy and legumes as the most frequent offenders.^{53, 54, 60, 62, 64, 65} Cow's milk has been identified as the most common food trigger for EoE. In one pediatric EoE cohort, cow's milk elimination alone improved peak esophageal eosinophil counts to below 15 eosinophils per hpf in 64% of patients, compared to 80% of patients treated with swallowed fluticasone.⁶⁶ Pediatric patients with milk-induced EoE have increased circulating total CD4⁺ Th2 cells and milk-specific Th2 cells; milk avoidance induces esophageal histologic remission.⁶⁷

A retrospective study demonstrated that milk-induced pediatric EoE patients could tolerate baked milk for at least 6 weeks, with 73% of patients maintaining histologic remission,⁶⁸ suggesting that thermally inactivated or food matrix bound milk antigenic epitopes might escape recognition by the immune system. Adult EoE patients can also tolerate extensively hydrolyzed cow's milk formulation, with 88.24% maintaining EoE remission.⁶⁹ While elimination diet is considered safe, it is not always palatable and can be cumbersome and expensive. In children, the potential for loss of tolerance in a food-specific IgE must be considered when utilizing an elimination diet. A case of anaphylaxis to milk after exclusion from diet for one year was reported in a pediatric patient with eosinophilic gastrointestinal disease after dairy product reintroduction.⁷⁰

Relevant biologic therapies

Infliximab and omalizumab, targeting TNF- α and IgE, respectively, have not been effective in treating EoE.⁶ Omalizumab appears to provide benefits to a subset of patients with low peripheral blood absolute eosinophil counts.⁷¹ Blockade of IL-5 with mepolizumab or reslizumab resulted in a significant reduction in peripheral eosinophilia, partially reduced esophageal eosinophilia, but did not alter esophageal fibrosis and demonstrated inadequate symptom response.³ Mepolizumab treatment of EoE children decreased the numbers of tryptase-positive cells, IL-9-positive eosinophils, and esophageal eosinophil-mast cell couplets. Following the mepolizumab trial, a reslizumab study in pediatric EoE patients was reported to improve histologic response, but symptom response was not significantly different from placebo treated children.⁷² QAX576, an anti-IL-13 monoclonal antibody, reduced esophageal eosinophilia and EoE-related gene expression, but did not significantly improve clinical symptoms.⁶ IL-13 blockade normalized expression of EoE-upregulated synaptopodin, an esophageal epithelial protein that regulates epithelial cell motility and barrier integrity.⁷³

RPC4046, another anti-IL-13 monoclonal antibody, reduced esophageal eosinophilia, but also improved endoscopic features and dysphagia in EoE patients, particularly in steroid-refractory EoE patients.⁶ This is consistent with the decreased in transcription of some remodeling genes including periostin for up to 6 months following treatment.⁷⁴ Dupilumab targets the common α chain of the IL-13 and IL-4 receptor and holds promise for EoE.

Combination therapy for EoE

Dual therapy with corticosteroid and elimination diet may be more effective in achieving clinical and histologic remission in some patients but has not been tested in a randomized, prospective manner.⁷⁵ In a retrospective study, combination therapy with topical corticosteroid, either swallowed aerosolized fluticasone or oral viscous budesonide, and TFED excluding only milk and soy for 3 months, followed by monotherapy with TFED only for 3 additional months achieved clinical remission with reduction in dysphagia.⁷⁶ However, histologic remission after 3 months of combined dual therapy was lost after corticosteroid discontinuation. The combination of elimination diet and topical corticosteroids has been demonstrated to decrease fibrosis in children.⁷⁷ Combination therapy with a PPI, lansoprazole, and oral viscous budesonide improved clinical symptoms and endoscopic and histologic features in 86.7% of pediatric EoE patients.⁶

Immunotherapy for treatment-resistant EoE

More recently, non-responders who fail swallowed corticosteroids, elimination diet, or dual combination therapy have been found to be more likely to be sensitized to perennial allergens such as dust mites, dog epithelia, and cat hair.⁷⁸ Non-responders to dual therapy with swallowed corticosteroids and elimination diet are more likely to exhibit allergen sensitization to mold or cockroach. These findings imply suboptimal control of persistent, chronic aeroallergen

antigenic stimulation of Th2 inflammation in treatment-resistant EoE patients, and suggest that allergen immunotherapy in sensitized individuals with EoE might represent a potential complementary strategy. Indeed, dust mite immunotherapy in a dust mite-sensitized pediatric patient has been reported to achieve EoE resolution.⁷⁹ The role of delayed allergic hypersensitivity, likely driven by antigen-specific T cells, is supported by the oral immunotherapy trials for foods which have been associated with new-onset EoE in up to 2.7% of patients with IgE-mediated allergy to food groups such as peanut, milk and egg.⁸⁰ In addition, a new-onset EoE can occur undergoing sublingual immunotherapy for aeroallergens.^{81, 82} These data underscore the importance of the route of antigen presentation in driving tissue eosinophil accumulation. Current trials to determine if food patch to milk can abrogate esophageal eosinophilia in milk-driven EoE are ongoing. Additional research and expert guidance from the allergist for optimization of the efficacy and safety of immunotherapy should provide another potentially useful approach for controlling treatment-resistant EoE.

Potential Emerging Therapies

Epithelial barrier disruption and the protease-rich milieu activate a program of IL-33, TSLP, and eotaxin-3/CCL26 expression in EoE that promotes Th2 immune activation and eosinophil infiltration.³ Infiltrating eosinophils secrete pro-inflammatory and pro-fibrotic cytokines, including IL-4, IL-5, IL-13, GM-CSF, and TGF- β 1. Animals models demonstrate that blockade of the IL-33/ST2 pathway can reduce experimental EoE, especially in its initiation phase.^{83, 84} In experimental EoE, blocking the TSLP receptor diminishes food impactions, and GM-CSF blockade reduces esophageal eosinophilia, basal cell hyperplasia and epithelial remodeling.³ Macrophage migration inhibition factor (MIF) is enriched predominantly in eosinophils on EoE biopsies and promotes eosinophil accumulation and tissue remodeling.⁸⁵

MIF blockade or genetic deficiency results in diminished esophageal inflammation and collagen deposition in a murine model of ovalbumin-induced eosinophilic esophagitis. Blockade of the MIF receptor, CXCR4, also reduces esophageal eosinophilia and collagen deposition. Antibody blockade with anti-Siglec-F has also shown promise in experimental EoE.³ A small randomized, double-blind, placebo-controlled trial of the selective CRTH2 antagonist OC000459 that inhibits prostaglandin D2-mediated eosinophil chemotaxis and activation showed modest reduction in eosinophil count and modest clinical symptom improvement in active, corticosteroid-sensitive or corticosteroid-resistant adult EoE patients after an 8-week course.⁸⁶

CONCLUSION

Current treatment strategies available to EoE patients center on monotherapy or combination therapy with dietary modification and corticosteroids to exclude antigenic stimulation of the Th2 immune cascades and to control tissue inflammation and pathologic tissue remodeling, respectively. The use of PPI is being suggested as a potential regimen to treat EoE, based on evolving understanding of PPI-REE. Dilation as a rescue therapy for the narrowed, fibrostenotic, symptomatic esophagus can potentially be avoided with optimal medical and elimination diet therapies. The molecular mechanisms underlying EoE pathogenesis are being unraveled, from which targeted therapies can be developed and evaluated in pre-clinical and clinical studies. Until then, current efforts focus on optimization of topical corticosteroid delivery, dosing, frequency, and duration of treatment, either alone or in combination with tailored elimination diet. The complexity of the treatment regimens and frequent follow ups require a multimodal, multi-disciplinary management approach for optimization of patient care.

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