

Emerging therapies for eosinophilic esophagitis



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Despite advances in the pathologic understanding of eosinophilic esophagitis (EoE), as of yet, no single agent has been approved by the US Food and Drug Administration to treat EoE. Off-label, EoE is currently treated by using the 3 Ds: drugs (particularly swallowed topical corticosteroids), dietary restriction, and endoscopic dilation. In the recent past, considerable progress in terms of EoE treatment has been made: (1) new EoE-specific steroid formulations optimizing mucosal deposition have been developed, which has culminated in recent approval of a budesonide effervescent tablet in Europe; (2) biologics used for other T_H2-mediated diseases, such as allergic asthma and atopic eczema, as well as purpose-developed biologics, have been studied in phase II trials in patients with EoE; and (3) novel dietary restriction strategies have evolved. Finally, further insights into the pathogenesis of EoE have revealed several novel disease mediators that might be targeted in the future. In the following article we will discuss recent advances in EoE treatment with regard to swallowed topical steroids, biological agents, dietary approaches, and novel molecular targets. (*J Allergy Clin Immunol* 2020;145:38-45.)

Key words: Eosinophilic esophagitis, treatment, steroids, diet, biologics

Eosinophilic esophagitis (EoE) is a chronic T_H2-mediated inflammatory disorder of the esophagus defined clinically by symptoms of esophageal dysfunction and histologically by an eosinophil-predominant infiltration of the esophageal mucosa.¹ Mechanistically, food and environmental factors interact with the esophageal epithelium, stimulating the release of proinflammatory cytokines, such as IL-33 and thymic stromal lymphopoietin (TSLP).² This leads to a T_H2-predominant response that orchestrates the production and release of IL-4, IL-5, IL-13,

Abbreviations used

BET: Budesonide effervescent tablet
 CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 cells
 EoE: Eosinophilic esophagitis
 Siglec-8: Sialic acid-binding immunoglobulin-like 8
 TSLP: Thymic stromal lymphopoietin

and TGF- β , which results in disruption of epithelial barrier function, tissue remodeling and eosinophil/mast cell infiltration. Intriguingly, next-generation single-cell RNA sequencing has recently revealed T-cell heterogeneity, with 2 subtypes, putative regulatory T cells and effector T_H2-like cells, being specifically enriched in patients with active EoE.³ The short-chain fatty acid receptor free fatty acid receptor 3 on these effector T_H2-like cells has been identified as a key mediator for amplification of the local T_H2 response in patients with EoE.³

Despite major advances in the understanding of EoE, medications have not yet been approved by the US Food and Drug Administration to treat EoE. Off-label, EoE is currently treated with drugs (particularly swallowed topical corticosteroids) and dietary restrictions that address the inflammatory response and esophageal dilation that ameliorates fibrostenotic consequences of disease. In the recent past, considerable progress in terms of EoE treatment has been made: (1) new EoE-specific steroid formulations optimizing mucosal deposition have been developed, with recent approval of a budesonide effervescent tablet (BET) in Europe; (2) biologics approved for T_H2-mediated diseases, including allergic asthma and atopic eczema, are undergoing phase II and III trials in patients with EoE; and (3) novel dietary restriction strategies have evolved. Furthermore, insights

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into the pathogenesis of EoE have revealed novel disease mediators that might be targeted in the future.

In the following article, we will discuss recent advances in EoE treatment with regard to swallowed topical steroids, biological agents, dietary restriction strategies, and novel molecular targets.

NEW STEROID FORMULATIONS

Efficacy of swallowed topical corticosteroids in the short-term treatment of EoE has long been proven.⁴ Steroids are one of the mainstays of EoE management and considered first-line treatment by many EoE specialists.

Topical corticosteroids act through various effects. For example, IL-13-induced pathways and genes, key pathogenic mechanisms in patients with EoE, are largely reversible by using steroid treatment.⁵ Further effects are reduction of esophageal eosinophilia, epithelial cell apoptosis and mast cell infiltration, downregulation of mast cell genes, and reduction in numbers of T cells and levels of proinflammatory cytokines, such as TNF.⁶ Topical corticosteroids can restore epithelial barrier function and positively affect tissue remodeling.^{4,7} Steroid compounds appear to have similar antieosinophil effects, as shown in a recent trial comparing outcomes in patients treated with 1 mg of oral viscous budesonide slurry administered twice daily or 880 µg of swallowed fluticasone powder administered twice daily (histologic response of 71% and 64% after 8 weeks of treatment, respectively).⁸ However, correct deposition on the epithelial surface layer is crucial to exhibit beneficial properties: viscous budesonide results in higher and longer exposure to the esophageal mucosa than does budesonide in a nebulized formulation.⁹ In addition, despite steroids' efficacy in the long term, medication nonadherence appears to be an issue.¹⁰ Therefore novel formulations have been developed in the recent past to increase mucosal contact time and simplify daily intake (Table I).

In Europe Miehke et al¹¹ studied 2 different formulations of budesonide effervescent tablets (BETs) for orodispersible use (1 mg twice daily and 2 mg twice daily) and a budesonide viscous suspension (2 mg twice daily) in a randomized controlled phase II trial. Histologic remission rates after 2 weeks of treatment were high with each formulation (100% BET 2 × 1 mg, 94.7% BET 2 × 2 mg, and 94.7% budesonide viscous suspension 2 × 2 mg) compared with placebo (0%). However, the orodispersible tablets (BETs) were preferred by 80% of patients.¹¹ Based on these findings, the orodispersible compound was further evaluated in 2 phase III trials (a short-term study in 88 adult patients and a long-term study in 204 adult patients). A 6-week course with 1 mg of BETs administered twice daily resulted in 58% clinicohistologic remission compared with 0% in the placebo group.¹² Extension for another 6 weeks in initial nonresponders increased the remission rates up to 85%.¹² In the long term a 48-week treatment with 1 mg of BETs administered twice daily and 0.5 mg of BETs administered twice daily was able to maintain clinicohistologic remission in 75.0% and 73.5% compared with 4.4% in the placebo group, respectively.¹³

In the United States a novel mucoadherent budesonide formulation (budesonide oral suspension) has been studied in a multicenter phase II trial (93 adolescent and adult patients). A 12-week treatment with 2 mg of budesonide oral suspension administered twice daily resulted in significant symptomatic improvement and induced histologic remission in 39% of patients compared with 3% in the placebo group.¹⁴ Efficacy was proven in

the long term also: an open-label extension study for 24 weeks revealed maintenance of histologic remission in 42%.¹⁵ Very recently, the phase III data were published in abstract form, demonstrating histologic and clinical responses in 53.1% and 52.6%, respectively (compared with placebo rates of 1% and 39.1%).¹⁶ In both the US and European studies, side effects were negligible, with no significant effect on serum cortisol levels and occurrence of esophageal candidiasis in only 2% to 11%. Finally, a dissolvable fluticasone tablet has also shown promising results in an early phase 1b/2a study.¹⁷

Recent insights into how long to treat patients with EoE come from the Swiss group. Cessation of steroid treatment in patients with deeply controlled disease (combination of clinical, endoscopic, and histologic remission for ≥6 months) resulted in a relapse in 81% within a median of 22 weeks.¹⁸ Similar results were seen in an observation phase of the above-mentioned budesonide versus fluticasone study.¹⁹ Therefore long-term maintenance treatment should be recommended. Dose reduction might be reasonable, as suggested by Butz et al²⁰ who showed that a 50% dose reduction in fluticasone was able to maintain complete remission in 73%,²⁰ although dose-finding trials are still lacking in the long term.

BIOLOGICS

Despite emerging data about the high efficacy of novel steroid formulations, several issues remain: a considerable proportion of steroid-refractory patients can still be observed; adherence rates to daily medication, particularly in the long term, are low; and response to steroids might be lost over time. In light of these limitations, biological agents targeting key cytokines, such as IL-4, IL-5, and IL-13, as well as IgE and TNF, have been studied for the treatment of EoE. Some of the drug development programs have successfully progressed to phase III trials (Fig 1).

Anti-IL-5

IL-5 is involved in eosinophil trafficking and eosinophil survival. Two anti-IL-5 antibodies, mepolizumab and reslizumab, have been studied for the treatment of active EoE with various degrees of success. Although a first study involving 4 adult patients suggested histologic and symptomatic response with mepolizumab, a subsequent randomized controlled trial in 11 adult patients demonstrated a significant decrease in esophageal eosinophilia by 54% and reduced levels of TGF-β as a marker of tissue remodeling but only minor symptomatic improvement.^{21,22} Similarly, a larger randomized controlled trial evaluating 3 different doses of mepolizumab in 59 children revealed a histologic response (89.5% with achieving a mean eosinophil count of <20 eosinophils per high-power field) but very limited clinical improvement (although it should be noted symptoms were not a primary outcome and validated measures were not used in this set of studies).²³

Similarly to mepolizumab, reslizumab treatment significantly reduced esophageal eosinophilia in a randomized controlled trial including 227 children and adolescents compared with placebo but without an effect on clinical activity judged by the blinded treating physician.²⁴ However, at one participating center, 6 patients continued with reslizumab as part of an open-label extension, and 4 continued through compassionate use. Over a follow-up of 9 years, Markowitz et al²⁵ demonstrated both

TABLE I. New steroid formulations specifically developed for the treatment of EoE

Compound	Studies	Outcome
BET	Short term: Double-blind RCT (n = 88), 6-week treatment course with 1 mg administered twice daily or placebo	Clinicohistologic remission: 58% vs 0% Histologic remission: 93% vs 0%
	Long term: Double-blind RCT (n = 204), 48-week maintenance treatment with 1 or 0.5 mg administered twice daily or placebo	Clinicohistologic remission: 75.0% vs 73.5% vs 4.4% Histologic relapse: 10.3% vs 13.2% vs 89.7%
Budesonide oral suspension	Short term: Double-blind RCT (n = 93), 12-week treatment course with 2 mg administered twice daily or placebo	Change in DSQ score: -14.3 vs -7.5 Histologic response rate: 39% vs 3%
	Long term: Open-label extension study for 24 weeks (2 mg once daily for 12 weeks and optional dose increase to 1.5-2.0 mg administered twice daily for 12 weeks)	Maintenance of remission in 42%, 4% of short-term nonresponders gained response

DSQ, Dysphagia symptom questionnaire; RCT, randomized controlled trial.

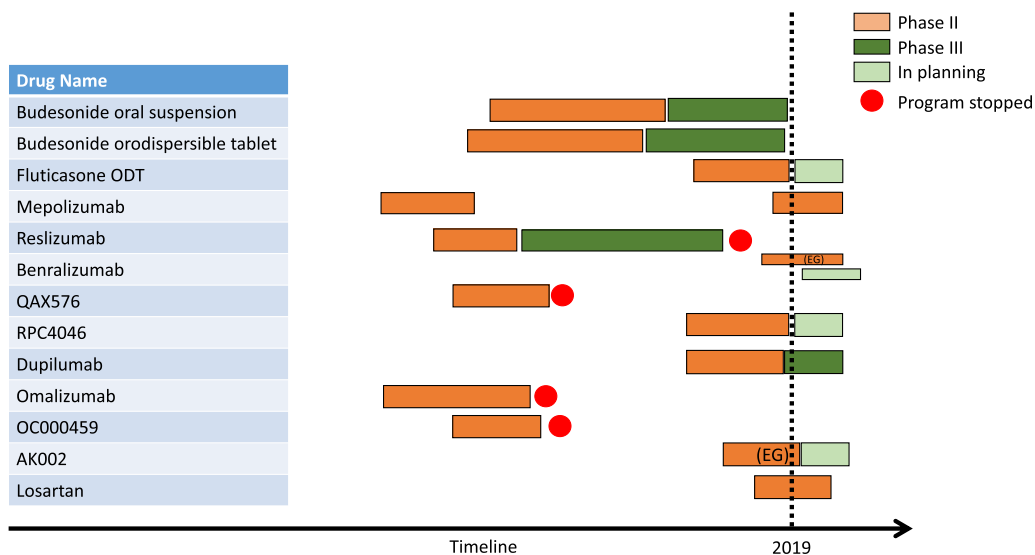


FIG 1. Development pipeline of EoE-specific programs over the last 2 decades with progression from phase II to phase III. EG, Eosinophilic gastritis.

histologic response (median eosinophil count, 35 vs 3 per high-power field) and considerable symptomatic improvement in terms of dysphagia, abdominal pain, heartburn, vomiting, and reflux. These data lack a control group and should therefore be interpreted cautiously.

Benralizumab, an eosinophil-depleting antibody that induces antibody-dependent cellular toxicity (through the IL-5 receptor α subunit) has been recently granted orphan drug designation for the treatment of EoE. Although no data from randomized controlled trials in patients with EoE are available thus far, in a small trial in patients with hypereosinophilic syndrome, a subset had gastrointestinal involvement with eosinophilia, which normalized after benralizumab treatment.²⁶

Anti-IL-13

IL-13 secreted by T_H2 cells is a key mediator in EoE pathogenesis. Studies have revealed markedly increased IL-13 mRNA levels in esophageal biopsy specimens from patients with active EoE compared with healthy control subjects. Of note, *in vitro* treatment of esophageal epithelial cells with IL-13 results in a

transcriptomic profile largely overlapping the EoE-specific transcriptome.⁵ IL-13 activates eosinophils and promotes eosinophil chemotaxis through increasing levels of eotaxin-3 and periostin.^{5,27} Two mAbs directly targeting IL-13 have been studied in patients with active EoE: QAX576 and RPC4046.

QAX576 was evaluated in a randomized controlled trial including 25 adult patients.²⁸ Although the trial did not meet the primary end point (>75% reduction in peak eosinophil counts), patients in the verum group showed a significant decrease in terms of esophageal eosinophilia (-60%) compared with patients randomized to the placebo group (+23%).²⁸ Furthermore, improvement in the EoE transcriptome was demonstrated with QAX576. In terms of symptomatic improvement, some trends were seen (decrease in frequency and severity of dysphagia), but overall, there was no significant effect of QAX576 on clinical disease activity (though this outcome was not primary).²⁸

In contrast to QAX576, a randomized controlled trial (n = 99) with the anti-IL-13 antibody RPC4046 (180 or 360 mg administered subcutaneously) resulted in a significant reduction in esophageal eosinophilia and endoscopic disease activity; there was also a strong trend toward reduction of dysphagia symptoms

($P = .07$).²⁹ It is notable that in this study half of the enrolled patients were previously refractory to topical steroids but had the same promising response rate to the biologic as the nonrefractory patients. Indeed, the validated EoE activity index patient-reported outcome score significantly improved in patients with previous steroid failure.²⁹ RPC4046 was also used in a 52-week-long open-label extension in which response was maintained for the treatment period, and the medication was generally well tolerated over this timeframe.³⁰

Anti-IL-13 and anti-IL-4 through inhibition of the shared IL-4 receptor α subunit

Similarly to IL-13, IL-4 has been shown to be a key driver in patients with T_H2 -mediated diseases. Through Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways, IL-4 leads to T_H2 cell differentiation and IgE class-switching in B cells.³¹ In patients with EoE, IL-4 is significantly upregulated in the esophageal mucosa and is among 8 key cytokines with increased levels in blood samples of patients with EoE that unambiguously differentiate patients with EoE from healthy control subjects.³² Dupilumab is a mAb that antagonizes both IL-4 and IL-13 because its target, the IL-4 receptor α subunit, is shared by both the IL-13 and IL-4 receptors and has been recently evaluated in a randomized controlled phase II trial including 47 adult patients.³³ Twelve-week treatment with dupilumab resulted in a significant symptomatic, endoscopic, and histologic improvement.³³

Anti-IgE and anti-TNF

Several findings encouraged use of anti-IgE antibodies and anti-TNF as treatment for active EoE: (1) EoE is frequently associated with IgE-mediated allergic diseases; (2) increased levels of IgE-positive cells are detected on biopsy specimens from patients with active EoE; and (3) TNF is highly upregulated in esophageal epithelial cells of patients with active EoE.³¹ Consistently, a first open-label trial in 15 patients with the anti-IgE antibody omalizumab showed promising results with a clinicohistologic remission in 33%.³⁴ However, a subsequent randomized controlled trial in 30 patients did not reveal any significant benefit with regard to symptoms and histologic disease activity after a 16-week treatment course.³⁵ Similarly, an open-label study including 3 male patients did not show any beneficial effect of the anti-TNF antibody infliximab.³⁶ Based on these small trials, use of omalizumab and infliximab for EoE is not supported.

SMALL MOLECULES

Several small molecules have been studied in the treatment of EoE. These therapies aim to target various inflammatory mechanisms, such as T_H2 cell function, mast cell degranulation, and eosinophil chemotaxis. Two small molecules were promising given their role in patients with allergic disorders, the mast cell stabilizer cromolyn sodium and the leukotriene antagonist montelukast, although both have not shown efficacy in randomized controlled trials in patients with EoE.^{37,38}

Given the key involvement of T_H2 cells in EoE pathogenesis and the high expression of chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2) on these cells, blocking CRTH2 appears to be a rational therapeutic approach. Straumann et al³⁹ evaluated the selective CRTH2

antagonist OC000459 in a randomized controlled trial including 26 patients. After an 8-week treatment, esophageal eosinophilic infiltration was significantly reduced (by 36%) in the treatment but not placebo group.³⁹ In addition, global assessment of disease activity by treating physicians improved with OC000459 but not with placebo.³⁹ However, patient-reported outcomes did not differ significantly between the 2 groups, and no effect on endoscopy was observed.³⁹ Because beneficial effects on eosinophilic infiltration are only modest and in light of more potent alternatives (steroids), this agent has yet to be evaluated any further in EoE management.

POTENTIAL MOLECULAR TARGETS

Based on *in vitro* findings and data emerging from studies in patients with other T_H2 -mediated disorders, numerous potential therapeutic targets have been suggested for EoE (Fig 2). When considering these agents, it should be realized that positive effects on eosinophils have to be contextualized with symptom and endoscopic improvements, ideally by using validated outcome measures. Ongoing or future clinical trials will answer the question of whether targeting these proposed targets have positive effects in terms of clinical, endoscopic, and histologic disease activity.

Integrin $\alpha4\beta7$

Integrin $\alpha4\beta7$ is involved in lymphocyte trafficking to the site of inflammation by binding to its counterpart, the adhesion molecule mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1), which is selectively expressed on endothelial cells in the intestinal tract. Vedolizumab, an anti-integrin $\alpha4\beta7$ antibody, blocks its interaction with mucosal vascular addressin cell adhesion molecule 1 and binds with high affinity to $CD4^+$ T cells and eosinophils. In addition, vedolizumab inhibits $\alpha E(CD103)/\beta7$ integrin, a marker of intraepithelial T lymphocytes.⁴⁰ Lately, Wen et al³ revealed that esophageal T_H2 cells are also αE positive. Thus $\alpha E(CD103)/\beta7$ integrin might serve as a therapeutic target in the future. Vedolizumab's potential role in EoE management has been suggested by 2 case reports of patients with concomitant inflammatory bowel disease and EoE, in which treatment resulted in clinical and histologic responses.^{41,42} Its antieosinophil effects have been further demonstrated in 2 case series on eosinophilic gastroenteritis.

Sialic acid-binding immunoglobulin-like 8

Sialic acid-binding immunoglobulin-like 8 (Siglec-8) is selectively expressed on eosinophils, mast cells, and basophils, with a key role in apoptosis.³¹ Preclinical data indicate the antieosinophil properties of anti-Siglec-8 antibodies. Two different anti-Siglec-8 antibodies were able to induce eosinophil cell death *in vitro*, particularly in the presence of IL-5 stimulation.⁴³ In mouse models treatment with anti-Siglec-8 resulted in depletion of IL-5-induced eosinophilia.⁴³ Moreover, anti-Siglec-8 antibody was shown to reduce both eosinophil and mast cell infiltration in the stomach and small intestine in a mouse model of eosinophilic gastroenteritis.⁴⁴ Very recently, a phase II trial evaluated the potential of anti-Siglec-8 (AK002) in patients with eosinophilic gastritis and enteritis, demonstrating depletion of gastrointestinal tissue eosinophilia and symptom improvement.⁴⁵ Data on AK002's efficacy in patients with EoE are currently not available.

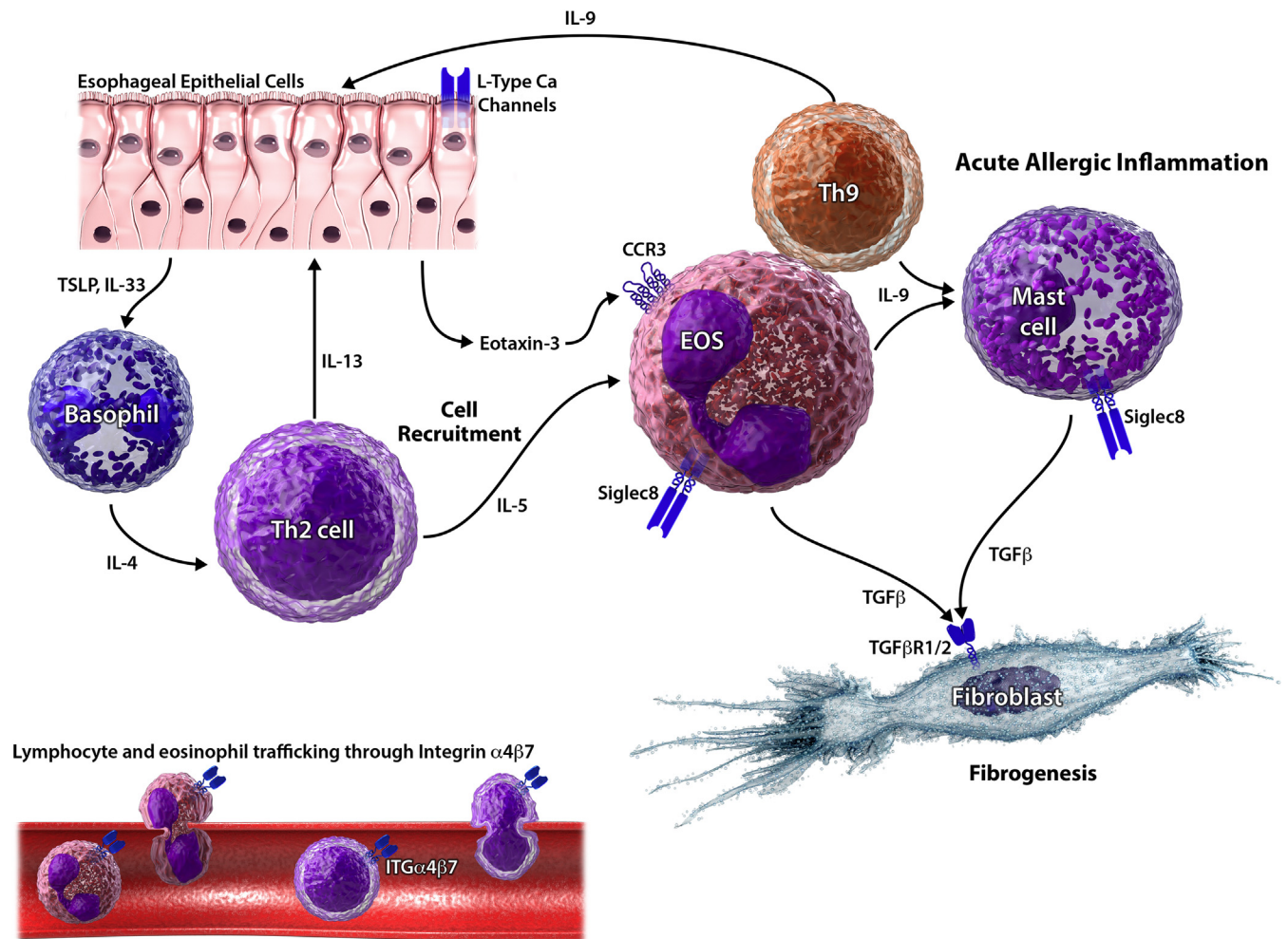


FIG 2. Potential therapeutic targets in patients with EoE. In a simplified model esophageal epithelial cell–released TSLP and IL-33 can trigger a T_H2 response through involvement of basophils and IL-4. T_H2 cells secrete IL-5, which, together with calcium channel–mediated eotaxin release from epithelial cells, results in eosinophil recruitment. Integrin $\alpha4\beta7$ is expressed on lymphocytes and eosinophils. By binding to its vascular counterpart, mucosal vascular addressin cell adhesion molecule 1, it mediates cell trafficking to the esophageal mucosa. Secretion of IL-9 (from eosinophils and T_H9 cells) further drives epithelial barrier disruption (together with IL-13 from T_H2 cells) and mast cell recruitment. Release of TGF- β (secreted by eosinophils and mast cells) perpetuates eosinophilic infiltration and drives tissue remodeling through activation of fibroblasts. Siglec-8 is selectively expressed on eosinophils and mast cells, with a key role in apoptosis.

TSLP

TSLP is an epithelium-derived cytokine that is upregulated in patients with active EoE.² It functions as a T_H2 switch and thereby promotes a T_H2 -weighted inflammatory response.³¹ Moreover, the chief EoE genetic susceptibility locus has been identified within the TSLP gene, suggesting a crucial role for TSLP in EoE pathogenesis.^{46,47} Anti-TSLP has been demonstrated to block esophageal eosinophilia and food impactions in murine models of EoE.⁴⁸ The TSLP antibody tezepelumab has been successfully studied in patients with severe uncontrolled asthma but has yet to be studied in patients with EoE.

TGF- β

TGF- β is known as a key regulator of fibrogenesis and has been shown to be involved in tissue remodeling and eosinophil recruitment in patients with EoE.⁴⁹ Therefore it represents an

interesting target to treat both the inflammatory and fibrostenotic aspects of EoE. Losartan, an angiotensin II receptor subtype 1 antagonist, can block TGF- β signaling and is currently studied in an open-label trial for EoE and eosinophilic gastroenteritis.⁵⁰

Calcium channels

Very recently, the calcium-channel blocker verapamil has been shown to attenuate IL-4–induced eotaxin expression in esophageal epithelial cells (*in vitro*).⁵¹ Thus calcium channels are a potential target to treat eotaxin-mediated eosinophil recruitment. No clinical data are available thus far.

Eotaxin receptor anti-CCR3

Eotaxin is a key driver of eosinophil recruitment to the esophageal mucosa. In mouse models CCR3 antibody has been

demonstrated to inhibit eosinophil inflammation and mucosal injury in patients with eosinophilic gastroenteritis.⁵² However, at least in asthmatic patients, a proof-of-mechanism study did not show efficacy of the CCR3 antibody AXP1275.⁵³

IL-9, IL-15, and IL-33

Several interleukins other than IL-4, IL-5, and IL-13 have been shown to be involved in EoE pathogenesis and are thus considered potential therapeutic targets: (1) IL-9 is a major driver of epithelial barrier disruption and mast cell recruitment, key events in EoE⁵⁴; (2) IL-15 expression is increased in the setting of human EoE and mediates EoE pathogenesis in *in vivo* models⁵⁵; and (3) increased IL-33 expression is associated with pediatric EoE, whereas exogenous IL-33 promotes EoE development in mice.² Anti-IL-9 has been studied in asthmatic patients, in whom it does not appear to be of significant effect. The anti-IL-15 antibody CALY-002 has been granted orphan drug designation for the treatment of EoE by the European Medicines Agency. However, clinical data for its efficacy in EoE treatment are not yet available. Similarly, there are no clinical data on the use of anti-IL-33 agents in patients with EoE.

NEW DIETARY APPROACHES

Because EoE is considered a food-triggered disorder, dietary restriction has been extensively studied as an EoE treatment modality. Despite the proven effectiveness of restrictive dietary approaches, such as the 6-food elimination diet, several issues remain: (1) introduction and maintenance of dietary restrictions can be challenging; (2) quality of life of patients and their families might be affected; and (3) multiple endoscopies are required to finally identify 1 or multiple food triggers. IgE-based allergy tests have demonstrated very limited accuracy in the prediction of food triggers in patients with EoE. Thus clinical use of empiric elimination diets is currently favored over allergy testing-directed diet therapy in patients with EoE.

Step-up approach

Given the limitations in use of empiric 6-food elimination diets, alternative strategies have been developed with the goal of less restrictive diets and greater efficiency in terms of food trigger identification. A 4-food elimination diet eliminating dairy, wheat, egg, and soy/legumes has been shown to be effective in 54% to 64%.⁵⁶ Because milk frequently represents the culprit food in children with EoE, cow's milk elimination attempts have been made. Recently, a randomized controlled trial in 63 children has shown similar histologic remission rates for milk elimination compared with a 4-food elimination.⁵⁷ Symptomatic improvement was seen in both groups, although to a greater extent in patients after the 4-food diet.⁵⁷ Because it appears reasonable to assume that less restrictive dietary strategies are also less effective, step-up strategies have been developed. The 2-4-6-food elimination approach resulted in remission rates of 43% after elimination of 2 foods.⁵⁸ Step-up in nonresponders to a 4-food and finally a 6-food elimination diet resulted in similar remission rates than previously reported. Moreover, endoscopic procedures and diagnostic processing time were reduced by 20%. More recently, a computer-based simulation revealed that a 1-3-food (dairy followed by wheat, egg, dairy elimination) and a 1-4-8-

food elimination step-up approach (dairy followed by wheat, egg, dairy, soy, and then wheat, egg, dairy, soy, corn, chicken, beef, and pork elimination) are most efficient in terms of culprit food identification.⁵⁹ Efficacy and efficiency of the latter 2 strategies have yet to be proven in clinical trials.

Targeted elimination

Because IgE-based allergy tests have not predicted response to elimination diets, novel strategies have been developed. Two of them show promising results. Based on evidence demonstrating an association of EoE with IgG₄, measurement of food-specific IgG₄ from esophageal biopsy specimens has been used to predict the response to dietary restriction.⁶⁰ Although there was high specificity for this strategy, sensitivities, particularly for peanuts and soy, were low. Diagnostic accuracy could be increased by adding a second test, a lymphocyte proliferation assay performed on patient serum. A positive response on either test resulted in agreement between tests and elimination diet results of 53% to 75%, which is considerably higher than for classical allergy test modalities. A more invasive approach reported by the Amsterdam group is the esophageal skin prick test, in which allergens are directly injected into the esophageal mucosa during upper endoscopy.⁶¹ Reaction of the esophagus was seen in 5 of 8 (immediate) and 2 of 8 (delayed) patients. Whether these reactions correlate with results from elimination diet strategies have yet to be determined.

FUTURE PERSPECTIVES

With increasing evidence for the efficacy of novel steroid formulations, as well as of emerging biological agents, the question will arise of where to position biological treatment. Looking at other inflammatory disorders, such as asthma and inflammatory bowel diseases, in which biological agents have been successfully introduced alongside topical steroid treatments, the following 3 positions within the treatment algorithm are conceivable for these agents: (1) treatment of steroid-refractory patients; (2) maintenance of steroid-induced remission; and (3) treatment of patients with EoE with atopic comorbidities.

At first glance and in light of histologic response rates of up to 93%, the relevance of steroid refractoriness appears to be limited with esophageal-specific formulations. However, significant heterogeneity in the short-term response rates to steroids has been noted with histologic efficacy of around 50% in some studies. Furthermore, response rates to steroid treatment are considerably lower in long-term studies, and loss of response might be a particular concern in chronic management.

In addition, need for daily intake can lead to medication nonadherence. Supervised and scheduled drug application every 2 to 4 weeks might result in better adherence and thus higher long-term remission rates. Moreover, biologic therapies might be an option for patients with several atopic comorbidities, in which T_H2 pathway-directed strategies could target multiple diseases with a single agent. This would obviate the need for multiple formulations of topical steroids (ie, swallowed for EoE, inhaled for asthma, and cutaneous for eczema).

Importantly, the optimal use of biologics in patients with EoE will undoubtedly be affected by the ongoing results of clinical trials regarding their long-term safety, efficacy, and cost. Characterization of EoE endotypes to predict future disease course,

need for aggressive treatment, and response to therapies will further help to personalize EoE management. Molecular fingerprinting of EoE using the EoE diagnostic panel has been demonstrated to identify 3 clusters of mRNA profiles associated with distinct phenotypes.⁶² Such stratification might pave the road to individually tailored treatment strategies and precision medicine in patients with EoE.

CONCLUSIONS

Newer formulations of swallowed topical corticosteroids have been shown to be highly efficacious in the short- and long-term management of EoE, which has led to the first approved EoE-specific treatment in Europe. In addition, several studies have proven the high efficacy of dietary approaches, which appears to be of similar magnitude as seen with steroids. However, empiric food elimination results in a very restrictive diet and a high endoscopic burden until the culprit food is identified. New approaches, such as the 2-4-6-food elimination diet (step-up approach), are similarly efficacious but more efficient. Despite high efficacy of steroid formulations and dietary restrictions, a considerable proportion of patients do not achieve or maintain clinicohistologic remission, particularly in the long term. Biological agents might be an effective treatment alternative, and anti-IL-13 and anti-IL-4 receptor antibodies are most promising with phase 2 data to date. Several newer targets have been identified and are currently being tested in clinical trials, such as the angiotensin II receptor type 1 (losartan) or Siglec-8 (anti-Siglec-8).

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