From Past to Present: The Evolution of Pharmacologic Therapies for Eosinophilic Esophagitis

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Abstract: Within the evolving landscape of eosinophilic esophagitis (EoE) management are multiple pharmacologic treatment modalities, including proton pump inhibitors (PPIs), swallowed topical corticosteroids, and novel biologic agents. Studies to date on PPIs and corticosteroids have provided valuable insights into how to define the disease, and recently approved biologic therapies are heralding a new era of EoE management. Although progress has been made in treating this complex inflammatory, fibrostenotic disease and in understanding its pathophysiology, several knowledge gaps persist and continue to be investigated. In addition, unknowns exist regarding the long-term safety and efficacy of new EoE treatments and how to position therapies in diverse patient populations. This article aims to provide historical context for the current landscape of pharmacologic treatments in EoE and perspectives on how future development may improve understanding and management of this complex disease.

Keywords
Eosinophilic esophagitis, pharmacologic treatments, proton pump inhibitors, swallowed topical corticosteroids, biologics

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by eosinophilic inflammation of the esophagus and symptoms of esophageal dysfunction such as dysphagia, food impaction, and reflux. First described in 1993, EoE has grown in prevalence and incidence, now affecting approximately 1 in 1000 people with both individual patient-level burdens and wider health care financial and economic burdens.[1-7] Left untreated, EoE can progress to cause complications such as esophageal strictures and fibrosis.[8] Current treatments include dietary therapies and various pharmacologic options, such as proton pump inhibitors (PPIs), swallowed topical corticosteroids, and biologics. Pharmacologic treatments are effective in reducing eosinophilic inflammation, symptoms, and mucosal damage; in decreasing the risk of future complications (ie, food impactions, stricture); and in improving health-related quality of life.[9-11] Despite multiple effective therapies, knowledge gaps remain in optimizing treatment approaches,

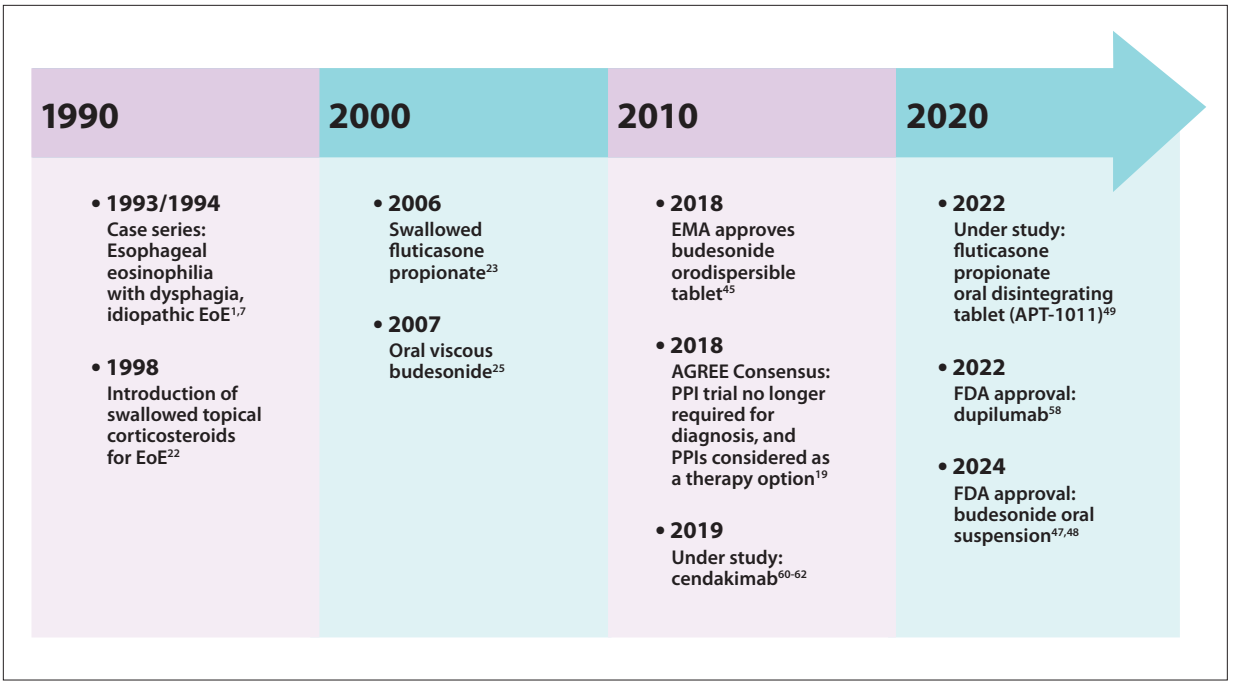

Figure. Timeline of pharmacologic treatments for EoE from the initial case series descriptions as esophageal eosinophilia with dysphagia (1993) and idiopathic EoE (1994).

EMA, European Medicines Agency; EoE, eosinophilic esophagitis; FDA, US Food and Drug Administration; PPI, proton pump inhibitor.

including how to choose a first-line treatment, predict response to specific treatments, assess disease severities and phenotypes, and prognosticate progression of disease. Addressing these gaps is essential to enhance personalized treatment strategies and ensure patients receive the most effective therapy early on. This article reviews the historical context and evolution of EoE therapies thus far, presents emerging targets, and highlights how these discoveries inform the understanding of this disease.

Eosinophilic Esophagitis Pharmacotherapies

Proton Pump Inhibitors

When EoE was first described in 1993 and further characterized in the early 2000s, a subset of patients with esophageal eosinophilia was found to have resolution of symptoms and histologic improvement with use of PPIs (Figure). Given the response to acid suppression, this new pathologic condition was thought to be a variation of gastroesophageal reflux disease (GERD) with eosinophilia, and the first consensus recommendations required exclusion of GERD using high-dose PPIs or pH monitoring to make a diagnosis of EoE.[12] As such, PPIs were employed as a diagnostic tool to differentiate EoE from GERD, with the assumption that a positive response to PPIs indicated GERD, whereas a lack of response suggested EoE. This dichotomy implied that GERD and EoE were mutually exclusive conditions.

In 2011, the term PPI-responsive esophageal eosinophilia (PPI-REE) was introduced to describe patients with esophageal eosinophilia who exhibited symptomatic and histologic resolution with PPI therapy.[13] This further complicated the diagnosis, as it suggested that PPI-REE was a distinct clinical entity, separate from EoE and GERD. Subsequent molecular studies, including RNA sequencing analyses, revealed that patients with so-called PPI-REE exhibited histologic and transcriptomic profiles like those of PPI-nonresponsive EoE patients, as well as clinical and endoscopic features. The findings indicated that both sets of patients had EoE with varying response to PPI therapy and prompted reassessment of its role in EoE.[14-16] Although the role of PPIs in EoE was initially thought to be only acid suppression, studies demonstrated that PPIs exert anti-inflammatory effects, including inhibition of T helper 2 (Th2) cytokines such as interleukin (IL)-4, IL-5, and IL-13. Inhibiting Th2 cytokines can reduce eosinophil recruitment, decrease eotaxin-3 expression involved in eosinophil migration, and potentially reinforce epithelial barrier function to reduce antigen penetration and subsequent immune activation.[17,18]

Together these findings marked a significant paradigm shift from the use of PPIs as a diagnostic tool to a therapeutic option in EoE, and the term PPI-REE fell

out of favor.[19] EoE is now defined by symptoms of esophageal dysfunction, histologic evidence of 15 eosinophils or greater per high-power field on esophageal biopsy, and the exclusion of other causes of esophageal eosinophilia.[20] PPIs are commonly recommended as part of first-line treatment given their relative ease of use, broad access, and relative low cost. However, because a subset of patients does not achieve disease remission with PPIs, further work is needed to elucidate mechanisms of PPI responsiveness and how to tailor effective treatments.

Swallowed Topical Corticosteroids

Given the understanding of EoE as an inflammatory condition, corticosteroids are another attractive treatment option. This was first demonstrated in 1998 by Liacouras and colleagues, with administration of oral methylprednisolone, which resulted in clinical improvement in 20 children with esophageal eosinophilia.[21] Recognizing the effectiveness of corticosteroid therapy but limitations of systemic long-term effects (eg, adrenal insufficiency, growth impairment, metabolic dysfunction), efforts to deliver treatment exclusively to the esophagus were explored. Faubion and colleagues were the first to report use of swallowed fluticasone propionate (FP) delivered by a metered-dose inhaler.[22] In a randomized, double-blind placebo-controlled study of children with EoE, Konikoff and colleagues demonstrated the efficacy of swallowed FP 880 mcg in achieving histologic remission.[23] A subsequent prospective randomized trial of 80 children with EoE comparing a 4-week course of oral prednisone vs swallowed FP showed histologic and clinical improvement in both groups, as well as symptom relapse after discontinuation of both therapies, highlighting not only the efficacy of corticosteroids for the treatment of EoE but also the need for maintenance treatment.[24]

In parallel to the study of swallowed FP, Aceves and colleagues demonstrated 80% histologic response, along with improvement in symptoms and endoscopic features, after treatment with oral viscous budesonide in children with EoE.[25] Given the availability of different swallowed topical corticosteroid formulations, Dellon and colleagues compared budesonide 1 mg twice daily delivered by nebulized vs oral viscous slurry in EoE with scintigraphy and demonstrated that increased mucosal contact time of the viscous slurry corresponded to higher efficacy, compared with the nebulized formulation.[26] Several studies later demonstrated the efficacy of swallowed FP and budesonide suspensions for children and adults, and this class of medication joined PPIs as a commonly used therapy for EoE.[10,27-30]

As corticosteroids became an effective and acceptable treatment for EoE, concerns regarding potential systemic exposure arose. Owing to favorable first-pass hepatic metabolism of swallowed topical corticosteroids, systemic bioavailability is low and systemic side effects are rare.[31] Although adrenal suppression with long-term use of swallowed topical corticosteroids has been reported, evidence is limited by heterogeneous definitions of the condition (eg, varied assessments of the adrenal axis, including serum, urine, salivary cortisol, adrenocorticotropic hormone [ACTH] stimulation test) and lack of symptom assessment from observational and randomized studies. As such, the risk of clinically significant adrenal suppression is unknown but likely low.[32,33] In a 4-year phase 3 open-label study of budesonide oral suspension (BOS; Eohilia, Takeda Pharmaceuticals) in EoE, adrenal insufficiency (defined by investigator's discretion) was reported in 2.3%, and abnormal ACTH stimulation test results in 8.4%; however, none of the patients with adrenal suppression had an abnormal ACTH stimulation test result.[34] Similarly, the risk of growth suppression, although likely small, is worth monitoring in children with EoE treated with swallowed topical corticosteroids. In a prospective open-label study of pediatric patients, growth impediment was not observed over a mean follow-up of 20.4 months, and after a 12-week randomized double-blind induction of BOS, a 24-week open-label extension study showed no decrease in sex-matched height; however, there was a trend toward decreased growth velocity.[35,36]

Given the effectiveness of swallowed topical corticosteroids at inducing and maintaining disease remission, preventing complications of stricture and food impaction, and improving patient quality of life, they have become an essential part of the EoE treatment armamentarium.[9,10,37] However, as an off-label therapy for EoE, use of swallowed topical corticosteroids (most commonly FP and budesonide) has been complicated by nonstandardized formulations and instructions, inappropriate administration, delayed access, unpredictable insurance coverage, and high financial costs.[38] At present, a 6-week course of budesonide (Pulmicort Respules, AstraZeneca) 1 mg twice daily (168 vials of 0.5 mg/2 mL) is estimated to cost $1033; in a recent cost analysis, the median cost was $2316 per quarter, a potentially unsustainable financial burden for maintenance therapy.[39,40] Similarly, a 6-week course of swallowed FP at 880 mcg twice daily induction dosing is estimated to cost $1355.[41] Off-label use requires that patients either self-mix budesonide respules into a viscous suspension (eg, honey, syrup, or sucralose) or swallow FP from an inhaler; alternatively, they could seek out costly compounding pharmacy services.[42-44]

Efforts to develop standardized formulations of swallowed topical corticosteroids for EoE led to the European approval of the first swallowed topical corticosteroid for EoE in 2018. The budesonide orodispersible tablet (BOT) dissolves quickly in the mouth without water, sparing

patients the inconvenience of self-mixing or compounding the medication. In a double-blind parallel study of adults with EoE, 58% on BOT 1 mg twice daily attained complete remission, defined by clinical and histologic factors.[45] Although BOTs are not currently available in the United States, BOS was recently approved by the US Food and Drug Administration (FDA). In a phase 2 trial of EoE patients aged 11 to 40 years, BOS was first studied as an induction treatment for 12 weeks and reached its coprimary endpoints of histologic response and symptom improvement.[46] A subsequent rigorous phase 3 trial similarly showed that compared with placebo, patients receiving BOS 2 mg twice daily attained histologic response (53.5% vs 1.0%; *P*<.001) and symptom response (52.6% vs 39.1%; *P*=.024) and had greater improvements in endoscopic severity.[47] As a result, BOS 2 mg/10 mL twice daily for 12 weeks was approved for treatment of EoE in people aged 11 years and older in 2024. Advantages of this premixed suspension not only include standardized, consistent dosing and viscosity but also convenient use for patients.[48] On the horizon, a FP oral disintegrating tablet (APT-1011) has demonstrated high response rates at various doses, potentially offering patients another treatment option.[49] Despite the expansion of effective EoE treatment options, it remains to be seen how approved and off-label swallowed topical corticosteroids will change the treatment landscape, as access continues to be limited by variable insurance coverage and out-of-pocket costs, concerns about dosing considerations for pediatric patients, and lack of comparative safety and efficacy data.

Biologics

The emergence of biologic therapies marks yet another paradigm shift in the history and management of EoE. The ability of biologics to target specific inflammatory processes offers a therapeutic path for patients who do not respond to conventional treatments (ie, PPIs, swallowed topical corticosteroids, and dietary therapies) and sheds light on the potential pathophysiology of EoE.

Given the pathologic eosinophilic inflammation characteristic of EoE, initial investigations targeted IL-5 and its role in regulating eosinophil proliferation and maturation. However, in a multicenter, randomized, double-blind, placebo-controlled trial of adolescents and adults with EoE, mepolizumab (Nucala, GlaxoSmithKline), a humanized anti–IL-5 monoclonal antibody, failed to achieve the primary endpoint of symptom improvement despite improvement in eosinophil counts and endoscopic severity.[50] Similarly, in a double-blind, randomized, placebo-controlled trial, reslizumab (Cinqair, Teva), another anti–IL-5 neutralizing antibody effective in treating asthma, demonstrated histologic response in children and adolescents with EoE, but no significant differences in symptoms were observed between treatment and placebo groups.[51] Efforts to investigate this pathway using benralizumab (Fasenra, AstraZeneca), an eosinophil-depleting anti–IL-5Rα monoclonal antibody, similarly demonstrated significant histologic response but no differences in symptoms or endoscopic findings in a phase 3 multicenter, double-blind, randomized, placebo-controlled trial of adolescents and adults.[52]

Further focusing on eosinophils as the primary target, lirentelimab (AK002, Allakos), a humanized immunoglobulin (Ig) G1 monoclonal antibody against Siglec-8 on the surface of mature eosinophils and mast cells, held promise for treatment of EoE and other eosinophilic gastrointestinal disorders. However, in the randomized, double-blind, placebo-controlled phase 2/3 study of adults and adolescents with EoE, lirentelimab demonstrated significant histologic response but did not reach the symptom endpoint.[53] This inconsistent success of biologics targeting eosinophils in EoE suggests that eosinophils alone may not be the primary driver of the disease.

Omalizumab (Xolair, Genentech and Novartis), a monoclonal anti-IgE antibody, has not been shown to be effective in EoE, suggesting that despite EoE's frequent comorbidity with atopic conditions, IgE does not play an important role in the pathogenesis of EoE.[54,55] Although tumor necrosis factor (TNF) can be found in esophageal tissue of EoE patients and is thought to synergistically affect IL-4–mediated eotaxin production, the anti-TNF antibody infliximab initially explored in EoE showed no significant histologic or clinical improvement.[56]

Although eosinophilic inflammation is a hallmark of EoE, there is growing evidence that the pathogenesis extends beyond eosinophils to involve a Th2 inflammatory response in the esophageal mucosa by promoting eosinophil survival, activation and degranulation, and dysregulation of the expression of key epithelial barrier regulatory genes that drive esophageal remodeling and clinical symptoms. In 2022, dupilumab (Dupixent, Sanofi and Regeneron), a monoclonal antibody inhibiting IL-4 and IL-13 signaling, became the first FDA-approved therapy for EoE in patients aged 12 years and older. In its phase 2 trial in adults with active EoE, dupilumab reduced symptoms of dysphagia, esophageal eosinophil count, and endoscopic severity and increased esophageal distensibility, compared with placebo.[57] The phase 3 trial in adults and adolescents with EoE demonstrated histologic remission (defined as strict cutoff of ≤6 eosinophils per high-power field) in 59% receiving weekly dupilumab and 60% receiving dupilumab every 2 weeks, compared with 6% in the placebo group, up to 24 weeks, with sustained remission to 52 weeks.[58] Because study inclusion criteria included PPI-nonresponsive patients and many participants who had previously also tried dietary restrictions or swallowed

topical corticosteroids, these findings suggest the potential for a response when other therapies fail. In a parallel phase 3 trial of children aged 1 to 11 years, dupilumab similarly resulted in significant improvement in histologic, endoscopic, and transcriptomic measures, compared with placebo.[59] In 2024, the FDA approval of dupilumab for EoE was expanded to include pediatric patients aged 1 year and older weighing at least 15 kg. Future studies will be crucial in identifying the long-term efficacy and safety of dupilumab in EoE. This approval marks a crucial advancement for EoE management, offering a new therapeutic option for patients who may not respond adequately to other pharmacologic or dietary treatments, but could also be considered as a first-line therapy in other patients. As such, positioning dupilumab in the management of EoE may be nuanced to include determination of disease severity, comorbid atopic conditions, prior treatments tried and responses, adherence, and patients' personal values and preferences. In addition to the long-term safety and efficacy of immunomodulation in EoE, other unknowns include how to predict nonresponse to dupilumab and how to ensure access to as well as insurance coverage for high-cost biologic therapy.

Further study of type 2 inflammatory targets, the role of IL-13 in eosinophil recruitment, esophageal barrier function, fibrosis, and remodeling is underway with cendakimab (Bristol Myers Squibb), a monoclonal anti–IL-13 antibody. A phase 2 randomized, placebo-controlled trial of adults with EoE demonstrated significant reduction in histologic and endoscopic features with cendakimab compared with placebo, and continued improvement or maintained response was noted through the 52-week long-term extension study.[60,61] The phase 3 trial evaluating the efficacy and safety of cendakimab in adolescents and adults with EoE is underway (NCT04753697).[62]

Despite their varying success, studies of biologic targets in EoE have highlighted important aspects of EoE pathophysiology. Eosinophilic inflammation plays a crucial role in disease presentation and progression; however, it may not be the sole driver of symptoms. Other underlying mechanisms, such as epithelial barrier dysfunction, esophageal remodeling, and interactions between various immune cells and cytokines, likely contribute to the development, presentation, and response to treatment of EoE.

Conclusion

The journey through 3 decades of pharmacologic discovery in the treatment of EoE underscores the significant advancements in the field: from the early use of PPIs as a diagnostic tool to acceptable therapy, to the use of off-label swallowed topical corticosteroids, and now to the emergence of targeted biologic therapies. Each milestone represents an important step toward understanding the pathophysiology of EoE and the unique challenges of disease management, especially how to tailor treatment to patients. Despite the advances in EoE pharmacotherapy, unmet needs remain, particularly in sustaining treatment efficacy, comparing effectiveness between therapies, and evaluating long-term outcomes. As the landscape of pharmacotherapies for EoE continues to evolve, future efforts should focus on accessibility to therapy and personalized strategies that support patient values and shared decision-making in the management of this chronic disease.

Disclosures

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