

Update on Emerging Pharmacologic Therapies for Patients With Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is a chronic immune-mediated condition identified by eosinophilic infiltration of the esophageal mucosa. Historically, pharmacologic options have been limited to proton pump inhibitors and swallowed topical corticosteroids, neither of which have been approved by the US Food and Drug Administration for the treatment of EoE. The goal of therapy is ultimately to avoid irreversible stricturing disease. Despite the rising prevalence of EoE, there have been few therapeutic advancements until recently. Some newer topical corticosteroid preparations are being studied, including a budesonide suspension (TAK-721), orodispersible tablet formulations of budesonide and fluticasone (APT-1011), and mometasone and ciclesonide preparations. Also in various stages of clinical trials are potential disease-modifying biologics such as dupilumab, cendakimab, lirentelimab, benralizumab, and mepolizumab. Some of these medications have proven efficacious for other atopic conditions and show incredible promise for the treatment of eosinophilic gastrointestinal diseases. Further studies will be needed to determine long-term treatment outcomes for each of these drugs.

Eosinophilic esophagitis (EoE) is a relatively new diagnostic entity compared with other conditions managed by gastroenterologists. EoE was first officially described in the literature in 1978 as a possible rare variant of eosinophilic gastritis,¹ and relatively little was known about this disease until the late 1990s. Over the past 20 years, knowledge about the pathogenesis of EoE has expanded rapidly, yet few treatment options exist. Although no US Food and Drug Administration (FDA)-approved treatments are currently available, a number of promising treatments for the management of EoE are on the horizon, including novel corticosteroid preparations and biologic agents.

Background

EoE is a chronic gastrointestinal (GI) disease characterized by eosinophilic infiltration of the esophageal epithelium. In EoE, T helper 2 (Th2)-mediated response triggered by antigens, likely in foods, stimulates

Keywords

Eosinophilic esophagitis, fluticasone, budesonide, mometasone, dupilumab, lirentelimab, cendakimab, benralizumab, mepolizumab

Table 1. Novel Corticosteroid Preparations for the Treatment of Patients With Eosinophilic Esophagitis

Medication	Formulation	Dosing	Response to Treatment
Budesonide	Oral suspension (TAK-721)	2 mg twice daily	53% histologic (≤ 6 eos/hpf) and symptomatic response after 12 weeks (phase 3 trial) ¹¹
	Orodispersible tablet	0.5-1.0 mg twice daily	73.5%-75.0% response rate (≤ 15 eos/hpf and symptom resolution) after 48 weeks (phase 3 trial) ¹⁴
Fluticasone	Orodispersible tablet (APT-1011)	1.5-3.0 mg twice daily	48%-86% histologic response rate (≤ 6 eos/hpf) after 12 weeks; 30%-84% sustained response at 52 weeks (phase 2b trial) ¹⁷
Mometasone	Swallowed aerosolization	200 μ g 4 times daily	Median Watson dysphagia score reduced by 6.5 ¹⁸
	Methylcellulose oral suspension	500-1500 μ g once daily	76% histologic response (≤ 15 eos/hpf) ¹⁹
Ciclesonide	Swallowed aerosolization	160-1280 μ g once daily	53% histologic response (< 15 eos/hpf) and 75% symptomatic improvement ²⁰

Eos/hpf, eosinophils per high-power field.

the release of proinflammatory cytokines interleukin (IL)-4, IL-5, IL-13, and transforming growth factor β , which results in eosinophil and mast cell infiltration, epithelial barrier disruption, and tissue remodeling.² Approximately 1 in 2000 people in the United States have EoE, and the incidence of EoE has been rising globally during the past 30 years at rates higher than what would be expected owing to increased awareness of this condition.³ Despite increasing incidence, management options have been quite limited until recently.

Current standard of care in the treatment of EoE involves either dietary restriction or pharmacologic therapy with either a proton pump inhibitor (PPI) or swallowed topical corticosteroid. Success rates of dietary therapy have varied widely: 45% with directed elimination approaches, 72% with 6-food elimination, and 90% with exclusive elemental formula in children.⁴ Although more restrictive diets have demonstrated a high success rate in achieving EoE remission, long-term adherence to dietary regimens can be difficult.⁵ Pharmacologic approaches to EoE have similarly mixed success. A meta-analysis by Lucendo and colleagues in 2016 examined PPI effectiveness in EoE and concluded an overall 50% histologic and clinical response rate.⁶ A meta-regression published by Cotton and colleagues in 2017 evaluated the effectiveness of swallowed topical corticosteroid therapies in achieving histologic response, resulting in an overall 77% response rate for budesonide and 68% response rate for fluticasone,⁷ making approximately one-third of patients with EoE corticosteroid nonresponders.

Novel Corticosteroid Therapies

Swallowed topical corticosteroids are the current standard of care in the pharmacologic treatment of patients with EoE, with studies dating back to 2006 demonstrating the efficacy of fluticasone and budesonide.^{8,9} Although these corticosteroids have traditionally been administered via swallowed aerosolization or a suspension mixed by the patient, lack of standardization of these medications is a significant concern, as the variety of mixing agents used are not specifically designed for esophageal delivery of medication, and inconsistencies in medication preparation and proper administration can lead to wide variability in effectiveness. As such, the field is in dire need of FDA-regulated, standardized medications for EoE treatment.

Several new corticosteroid formulations have been reported recently (Table 1). TAK-721 is a budesonide oral suspension (BOS; Takeda). Although TAK-721 was granted FDA Priority Review in December 2020, the FDA recently announced that it would not approve the formulation without further study.¹⁰ Recently published results from a phase 3 trial showed that treatment with BOS 2 mg twice daily (BID) resulted in a 53% histologic (≤ 6 eosinophils per high-power field [eos/hpf]) and symptom response rate in adolescents and adults after 12 weeks.¹¹ Secondary analysis of phase 2 data showed evidence of improvement in both dysphagia and pain scores in patients treated with BOS.¹² Recent data demonstrated a reduction in relapse rates in initial responders who were

continued on BOS for 36 weeks vs those switched to placebo.¹³

The European Medicines Agency has approved an orodispersible tablet formulation of budesonide (BOT; Jorveza, Dr Falk Pharma) for the treatment of EoE, after a phase 3 study demonstrated its effectiveness in inducing remission in adults with active EoE.¹⁴ After 48 weeks of treatment, BOT was effective in achieving and maintaining complete remission (defined as symptom resolution and ≤ 15 eos/hpf on esophageal biopsy) in more than 70% of patients. Candidiasis, which resolved with treatment, was suspected in up to 16% of patients receiving BOT. This study follows a previous phase 2 study completed by the same group, which both showed effectiveness of treatment and established that a higher percentage of patients preferred the BOT formulation over traditional budesonide viscous suspensions (80% vs 17%).¹⁵ More recently, Lucendo and colleagues also demonstrated improved distensibility in patients who underwent a 6-week treatment course of BOT 1 mg BID vs patients who received placebo ($P=.004$).¹⁶ This distensibility further increased in patients who continued on BOT 1 mg or 0.5 mg BID over the following 48 weeks of treatment vs those receiving placebo ($P=.021$).

A novel oral disintegrating tablet formulation of fluticasone (APT-1011; Ellodi Pharmaceuticals) is in phase 3 trials and was granted Fast Track designation by the FDA in February 2021. Preliminary phase 2 data showed that APT-1011 is highly efficacious for treatment and maintenance of histologic remission (≤ 6 eos/hpf) in adults with EoE over 52 weeks, with as many as 86% of patients achieving histologic response at 12 weeks (80% 3 mg BID; 67% 3 mg at bedtime [HS]; 86% 1.5 mg BID; 48% 1.5 mg HS; and 0% placebo response rates).¹⁷ Sustained remission was achieved in up to 84% of patients who responded at 12 weeks. Of those patients who did not respond at 12 weeks, 26% achieved histologic remission with ongoing treatment with APT-1011 3 mg BID by week 52. Symptomatic and endoscopic improvements were also noted in all treatment groups and were sustained at 52 weeks. The most common side effect was oral/esophageal candidiasis in 12% of patients.

Studies evaluating alternative corticosteroid preparations with theoretically lower systemic bioavailability than fluticasone and budesonide have also been published. A recent study from Sweden was the first randomized controlled trial to document the effectiveness of mometasone in treating symptoms of EoE in adult patients.¹⁸ This study utilized swallowed mometasone spray 200 μ g 4 times daily for 8 weeks. Mometasone demonstrated a significant effect on patient-reported dysphagia symptoms vs patients who received placebo; however, the study found no significant difference in health-related quality-of-life

(HRQOL) scores and did not evaluate histologic findings. A prior retrospective study utilizing swallowed mometasone in a methylcellulose suspension in 34 pediatric and young adult patients with EoE demonstrated histologic response (≤ 15 eos/hpf) in 76% of patients, including 72% of patients with prior treatment failure on other corticosteroid formulations.¹⁹ The effectiveness of ciclesonide in EoE was also recently documented in a retrospective cohort study of 81 patients.²⁰ This study reported a significant improvement in symptoms, including dysphagia, abdominal pain, vomiting, heartburn, and behavior changes, in 75% of patients. Improvement in endoscopic findings of EoE and reduction in peak esophageal eosinophil counts were also demonstrated. Remission (< 15 eos/hpf) was achieved or maintained in 53% of patients. Furthermore, 29% of patients with a history of persistent inflammation despite initial treatment with budesonide or fluticasone achieved remission on ciclesonide, and a 60% response rate was observed in those who were corticosteroid naive.

Biologics Under Investigation

Recently, there has been an influx of biologic medications that target the Th2 inflammatory cascade (Table 2). Many of these biologics have demonstrated effectiveness and have been approved by the FDA for the treatment of several allergic diseases, although these medications are not currently approved for the treatment of EoE.

Dupilumab (Dupixent, Sanofi and Regeneron) is a monoclonal antibody that acts at the level of the shared IL-4 receptor α subunit to inhibit the action of pro-inflammatory cytokines IL-4 and IL-13. Dupilumab is currently approved by the FDA for use in moderate-to-severe atopic dermatitis, asthma, and rhinosinusitis with nasal polyposis. It is now in phase 3 clinical trials in both adults and children for the treatment of EoE and was granted Breakthrough Therapy designation for EoE by the FDA in late 2020. A recent study evaluating Th2 inflammatory biomarkers in clinical trials in patients with atopic dermatitis, asthma, and EoE showed that dupilumab suppressed most Th2 inflammatory biomarkers, including rapid inhibition of serum thymus and activation-regulated chemokine, plasma eotaxin-3, and serum periostin, with more gradual reduction in total immunoglobulin E levels and significant decrease in blood eosinophils in EoE specifically.²¹ Results of phase 2 trials in adults with EoE demonstrated significant reduction in eosinophil counts, with 83% of patients achieving less than 15 eos/hpf after 12 weeks of weekly subcutaneous dupilumab injections, along with significant improvement in endoscopic features of EoE and esophageal distensibility vs placebo.²² Dupilumab treatment was associated with significantly

Table 2. Biologics Under Investigation for the Treatment of Patients With Eosinophilic Esophagitis

Medication	Mechanism of Action	FDA-Approved Indications	Eosinophilic Esophagitis Clinical Trial Status
Dupilumab	Monoclonal antibody to IL-4 receptor α subunit	Atopic dermatitis, asthma, rhinosinusitis with nasal polyposis	Phase 3 trials ongoing
Cendakimab	Monoclonal antibody to IL-13 receptor	None	Phase 3 trials ongoing
Lirentelimab	Monoclonal antibody to Siglec-8	None	Phase 2/3 trials ongoing
Benralizumab	Monoclonal antibody to IL-5 receptor	Asthma	Phase 3 trials ongoing
Mepolizumab	Monoclonal antibody to soluble IL-5	Asthma, hypereosinophilic syndrome, chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis	Phase 2 trials ongoing

FDA, US Food and Drug Administration; IL, interleukin; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8.

improved dysphagia symptoms vs placebo, with some patients demonstrating significant changes as early as week 1. Preliminary data from part A of a phase 3 study demonstrated improvement in disease-specific HRQOL and symptom burden in adolescent and adult patients after 24 weeks of weekly dupilumab treatment.²³ Furthermore, recently presented data from the extension portion of the phase 3 trial demonstrated that patients who either received dupilumab for an additional 28 weeks (dupilumab-dupilumab) or switched from placebo to dupilumab for 28 weeks (placebo-dupilumab) showed a similarly high rate of histologic response, with 55.9% and 60% achieving less than 6 eos/hpf, respectively, and 82.4% and 70% achieving less than 15 eos/hpf, respectively, at week 52.²⁴ Participants also demonstrated improvement in dysphagia symptom score and improvement in endoscopic findings.

Cendakimab (previously RPC4046; Celgene) is a monoclonal antibody that inhibits binding at the IL-13 receptor. A 16-week phase 2 study in adults with EoE demonstrated improved esophageal eosinophil count and endoscopic findings after weekly subcutaneous injections.²⁵ Although this study did not meet statistical significance regarding dysphagia improvement, a trend toward improvement was observed with the higher dose. Data from the open-label, long-term extension (LTE) demonstrated continued improvement in endoscopic, histologic, and clinical measures of EoE disease activity past the 12-week induction phase.²⁶ A significant decrease in eosinophil counts in all treatment groups was maintained for the duration of the 52-week study, and the proportion of responders (peak eos/hpf <15) increased from week 12 to week 52 in all groups. In contrast to the initial phase 2 study, significant symptomatic response was also

demonstrated, with symptom remission rates rising in both the placebo-cendakimab patients (14% at LTE entry to 67% at LTE week 52) and cendakimab-cendakimab patients (30% at LTE entry to 54% at LTE week 52). A subgroup analysis of 44 corticosteroid-refractory patients was also performed and found no notable differences in any measure vs the entire study population.

Lirentelimab (previously AK002; Allakos) is a monoclonal antibody to sialic acid-binding immunoglobulin-like lectin 8, a CD33 receptor found on the cell surface of eosinophils and mast cells. Lirentelimab selectively induces apoptosis and antibody-dependent cellular cytotoxicity of activated eosinophils and inhibits mast cell activation. Data from a phase 2 trial in eosinophilic gastritis and duodenitis (EG/EoD) demonstrated a 97% reduction in GI tissue eosinophilia and a 58% reduction in total symptom score vs placebo,²⁷ and preliminary data demonstrated sustained histologic and symptomatic improvements in patients with EG/EoD through week 94.²⁸ Of the 65 adult patients in the phase 2 EG/EoD trial, 35 patients had concomitant EoE. A prespecified analysis involving 23 patients with esophageal eosinophilia at screening showed that 13 of the 14 patients treated with lirentelimab achieved histologic remission (≤ 6 eos/hpf) vs only 1 of the 9 patients in the placebo group. The treatment group also reported a 53% reduction in dysphagia symptoms at 14 weeks vs 17% in the placebo group.²⁷ In a December 2021 press release, Allakos announced that although the 24-week phase 3 EG/EoD trial and phase 2/3 EoE trials met their histologic coprimary endpoints, the trials did not achieve statistical significance for the patient-reported symptomatic coprimary endpoints; however, results of these trials have not yet been published.²⁹

Benralizumab (Fasenra, AstraZeneca) is a monoclonal antibody directed against the membrane-bound IL-5 receptor α chain present on eosinophils. IL-5 is a proinflammatory cytokine involved in the differentiation and maturation of eosinophils, allowing for eosinophil survival and migration from the bone marrow. Benralizumab is currently approved by the FDA for the treatment of severe asthma in patients 12 years and older and was granted orphan drug status for EoE by the FDA in 2019. A phase 2 study published in 2019 evaluated the effectiveness of benralizumab in patients with platelet-derived growth factor receptor α -negative hypereosinophilic syndrome, in which a subgroup analysis of patients with concomitant eosinophilic GI disease identified 2 patients with EoE, both of whom demonstrated complete histologic remission (0 eos/hpf) at follow-up endoscopy at 24 weeks.³⁰ Phase 3 trials of benralizumab in EoE are currently underway.

Mepolizumab (Nucala, GlaxoSmithKline) is another biologic that blocks IL-5 activity, specifically against soluble IL-5. Mepolizumab is currently approved by the FDA for severe asthma in patients 6 years and older, hypereosinophilic syndrome in patients 12 years and older, chronic rhinosinusitis with nasal polyps, and eosinophilic granulomatosis with polyangiitis. An open-label phase 1/2 study of 4 patients with EoE in 2006 showed inconsistent symptom improvement, although there was improved endoscopic characteristics and significant reduction in esophageal eosinophilia.³¹ Little has been published on mepolizumab in EoE since then, but phase 2 trials are currently underway.

Conclusion

Dietary restrictions, PPI therapy, and swallowed topical corticosteroid preparations have long remained the mainstays for EoE treatment. Currently, several novel corticosteroid preparations, along with potential disease-modifying biologic therapies, are on the horizon as potential treatments for EoE, a disease with limited treatment options. Further studies will be needed to determine the long-term outcomes of these drugs, but they provide tremendous promise for altering the course of eosinophilic GI diseases.

Disclosures

Boston Children's Hospital is a study site for phase 3 trials titled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients With Active Eosinophilic Esophagitis (EoE) (EoE KIDS) (ClinicalTrials.gov Identifier: NCT04394351; sponsored by Regeneron Pharmaceuticals) and A Study of Lirentelimab (AK002) in Patients With Active Eosinophilic Esophagitis (KRYPTOS)

(ClinicalTrials.gov Identifier: NCT04322708; sponsored by Allakos). Although the authors are listed as subinvestigators in these trials, neither author is receiving financial compensation from these studies or has any other competing financial interests.

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