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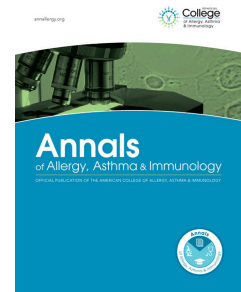
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Future Therapies for Eosinophilic Gastrointestinal Disorders

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1 Introduction

Over the past decade, significant progress has been made in the field of eosinophilic gastrointestinal diseases (EGIDs). Refined diagnostic guidelines as well as development of standardized approaches to patient reported outcomes (PROs) and endoscopic and histologic assessments has paved the way to improvements in diagnosis and outcomes. The mechanisms of disease, especially in eosinophilic esophagitis (EoE), are better understood and have lead to identification of an increasing number of potential treatment targets. Non-esophageal EGIDs (neEGIDs) including eosinophilic gastritis (EG), gastroenteritis (EGE), and colitis are relatively lesser understood, but several novel therapeutics are under development for these uncommon disorders as well.¹ Despite this progress, there currently are no Food and Drug Administration (FDA)-approved medications for treatment of any EGID. Current commonly used treatments includes proton-pump inhibitors (PPIs), swallowed/topical corticosteroids, and food elimination diets.² Although each of these options are effective, there are limitations. Swallowed/topical corticosteroids can control eosinophilic inflammation in 70-80% of those with EoE, but steroid resistance, as well as loss of responsiveness, can be seen, occurring in as many as 75% of cases.³⁻⁵ Food elimination diets can be effective in a similar percentage of patients, though there are no current tests that can accurately and preemptively identify the triggering food(s), and long-term dietary adherence can be difficult.⁶⁻⁸ Given these factors, improved therapeutic options are needed. With the progress made in understanding disease mechanisms, a variety of novel treatments are being investigated with several in late phase clinical trials (**Table 1**). In this article, the most promising of these potential therapies will be reviewed.

Identifying Targets for Treatment

Significant work has been performed over the past 20 years to gain a better understanding of the genetics, environmental modifiers, and pathophysiology of EGIDs. **(Figure 1)** EoE, and likely neEGIDs, are driven by T-helper type 2 (Th2) cell response leading to increased production of allergic cytokines including interleukin (IL)-4, IL-5, and IL-13.⁹⁻¹¹ T-cell activation may be at least partially mediated through thymic stromal lymphopoietin (TSLP).¹² IL-5 is particularly important for eosinophil development, trafficking, and activation, and is produced in larger amounts in patients with EoE compared to controls.¹³⁻¹⁵ While both IL-4 and IL-13 also play a role in eosinophil activation, these also serve to activate basophils and mast cells, the exact function of which remains to be determined in EGIDs.¹⁶⁻¹⁸ IL-4 and IL-13, along with eotaxin-3 and chemoattractant receptor expressed on Th2 cells (CRTH2), also play important roles in chemotaxis of eosinophils.¹⁹⁻²⁰ Integrins may play a particular role in homing of eosinophils to gastrointestinal tissues, while sialic acid-binding immunoglobulin-type lectins (Siglecs) help with eosinophil binding to the cell surface.²¹⁻²⁴ IL-13 also serves as a critical mediator of epithelial barrier disruption by activating CAPN14 and SPINK7 genes which leads to decreased production of filaggrin and desmoglein-1, important promoters of epithelial integrity.²⁵⁻²⁹ Barrier disruption leads to trans-epithelial passage of antigenic proteins which can further disease activity and eosinophilic-driven inflammation. Over time, transforming growth factor (TGF- β) activation leads to tissue fibrosis with resulting remodeling.³⁰⁻³¹ With elucidation of these mechanisms, a variety of novel therapeutics have been developed in attempts to modify these processes, restore barrier integrity, reduce tissue eosinophil burden, and improve clinical outcomes **(Figure 2)**.

Biologic Therapies

IL-4

Dupilumab is a monoclonal antibody that binds to the α -subunit of the IL-4 receptor with resulting blockage of both the IL-4 and IL-13 pathways and appears promising for modifying EoE. Dupilumab is currently approved in the U.S. to treat asthma and eczema. In a phase 2 clinical trial completed in 2017, 47 adult subjects with EoE were randomized to receive dupilumab (600mg loading dose, followed by 300mg weekly) or placebo for 12 weeks. Subjects treated with dupilumab had significant improvements in dysphagia, endoscopic findings, and peak eosinophil counts compared to placebo.³² A phase 3 clinical trial in EoE for adults and adolescents is currently enrolling with an estimated completion date of 2023 (ClinicalTrials.gov Identifier: NCT03633617). Dupilumab is also being investigated for use in eosinophilic gastritis (EG). (ClinicalTrials.gov Identifier: NCT03678545)

IL-13

To date, two EoE trials have been completed utilizing IL-13 antibodies. The first molecule studied was QAX576, which inhibits IL-13 activity and eotaxin production through direct binding to the IL-13 molecule. In a randomized, placebo-controlled trial of 23 adults with EoE, treated subjects demonstrated a 60% reduction in mean proximal/distal esophageal eosinophils compared to only 23.3% reduction in the placebo group.³³ The second molecule, RPC4046, which prevents IL-13 binding at both receptor subunits IL-13-R α 1 and IL13R α 2, was investigated in a phase 2, randomized, placebo-controlled trial. Ninety-nine adult subjects received RPC4046 (180mg or 360mg weekly) or placebo for 16 weeks. RPC4046 led to significant reductions in mean esophageal eosinophil counts with more than 50% of treated

subjects demonstrating <15 eos/hpf at end of study compared to none in the placebo group. Treated subjects also had significant improvement in endoscopic and histologic scoring as well as patient perceived measures of disease severity.³⁴ A subgroup analysis of steroid-refractory patients demonstrated similar reductions in eosinophil counts as steroid-responsive subjects as well as improvements in endoscopic and histologic findings suggesting this drug may serve as a suitable alternative in steroid resistant patients. Additional trials are anticipated.

IL-5

Several monoclonal antibodies that target IL-5 have been developed, including mepolizumab, reslizumab, and benralizumab. Each of these drugs are approved for treatment of eosinophilic asthma. Mepolizumab and reslizumab act through direct binding to the IL-5 molecule while benralizumab binds to the α -subunit of the IL-5 receptor. The first trial of an anti-IL5 drug in EoE was published in 2006 and has been followed by two randomized clinical trials.³⁵⁻³⁷ The initial study by Stein et al. demonstrated a 8.9-fold reduction in mean tissue eosinophils as well as a 2-fold reduction in mast cell density and epithelial hyperplasia after treatment with mepolizumab. Treated subjects also had improvements in clinical symptoms, endoscopic findings, and even reductions in peripheral blood eosinophilia.³⁵ In a subsequent randomized clinical trial of mepolizumab performed by Straumann et al., investigators sought to determine the number of subjects who achieved the primary endpoint of <5 eos/hpf after treatment, compared to placebo.³⁶ Eleven adults were enrolled but none achieved the primary endpoint, nor did any subject achieve reductions in esophageal eosinophils to <15 eos/hpf. Those treated with mepolizumab did demonstrate at least a 65% reduction in peak eosinophils and a 67% reduction in mean eosinophils compared to no such reductions in the placebo group.

Symptoms and endoscopic findings also improved in the mepolizumab group, but this change was not statistically significant. In the second mepolizumab trial, 59 children were randomized to mepolizumab at three different doses: 0.55mg/kg, 2.5mg/kg, or 10mg/kg over a period of 12 weeks.³⁷ The primary outcome in this study was the number of subjects who achieved a peak esophageal eosinophil count <5 eos/hpf at the end of study. Less than 10% of subjects achieved the primary outcome although nearly 90% did achieve reductions in mean eosinophil counts to <20 eos/hpf. Symptoms and endoscopic findings did not significantly change during the study period. The efficacy of reslizumab in EoE was studied in a trial of 226 children and adolescents who were randomized to receive reslizumab at 3 different concentrations (1mg/kg, 2mg/kg, 3mg/kg) or placebo over 4 months. The treatment group demonstrated significant reductions in peak esophageal eosinophil counts compared to placebo, although there were no significant differences in regards to clinical symptoms or quality of life measures.³⁸ Six subjects from the original cohort were treated for an additional 6-7 years and demonstrated improvement in clinical symptoms and mean esophageal eosinophil counts compared to placebo.³⁹ No trials of benralizumab in EGID have been completed to date, although a placebo-controlled trial in adolescents and adults with EG is currently enrolling (ClinicalTrials.gov Identifier: NCT03473977) and a trial for EoE is being developed. In a randomized trial of benralizumab versus placebo in 24 subjects with hypereosinophilic syndrome, seven subjects had GI tract eosinophilia; all had near complete resolution (≤ 1 eos/hpf), regardless of location, suggesting that benralizumab may be effective in EGIDs.⁴⁰

Siglec-8

As reviewed earlier, siglecs play an important role in cell signaling and immune system regulation. Siglec-8 in humans is preferentially expressed by eosinophils, basophils, and mast cells.⁴¹ In mice, anti-siglec-F antibodies, the murine equivalent of siglec-8 in humans, demonstrated reductions in gastrointestinal eosinophils, Th2 cytokines, and IgE levels, as well as improvements in weight.⁴² In a mouse model of EoE, anti-siglec-F antibodies were associated with significant reductions in esophageal eosinophils compared to controls as well as reductions in blood and bone marrow eosinophils. Treated mice also demonstrated decreased angiogenic cytokines and fibronectin deposition.⁴³ A siglec-8 antibody, AK002, has recently completed a phase 2 randomized, controlled study in adults with EG/EoE. The study sought to determine the number of subjects who had a >75% reduction in tissue eosinophil counts from gastric or duodenal biopsies after treatment for 4 months. Secondary endpoints included a >30% reduction in clinical symptom scores. At the end of study, treated subjects demonstrated a 95% reduction in tissue eosinophils compared to a 10% increase in controls. There were significant reductions in symptom scores in the treated group compared to controls. Interestingly, 14 of the 39 treated subjects had concomitant EoE and 13 of these 14 subjects also had reductions in esophageal eosinophils to <5 eos/hpf compared to such findings in only 1 of 9 placebo subjects.⁴⁴ A phase 3 study in EG and a phase 2 study in EoE are planned.

Integrins

Integrins play an important role in eosinophil trafficking to GI tissues, especially the small intestine and colon. Vedolizumab is a monoclonal antibody that binds directly to $\alpha 4\beta 7$ integrin on lymphocytes and inhibits binding of these lymphocytes to MadCAM-1 and fibronectin found on endothelial cells. Initially vedolizumab was developed for use in inflammatory bowel disease

(IBD) but in a report by Nhu et al., an adult patient with Crohn's disease and concomitant EoE had noted resolution of EoE after treatment of their IBD with vedolizumab.⁴⁵⁻⁴⁶ In a retrospective case series by Kim et al., 5 patients with EG or EGE were treated with vedolizumab. Four of the 5 patients were able to wean or stop dosing of systemic steroids used to control their EGID and 40% had improvements in clinical symptoms.⁴⁷ In a larger retrospective cohort of 22 patients with EGE, vedolizumab was effective at reducing clinical and histologic findings in steroid-resistant patients.⁴⁸ There are no current clinical trials of vedolizumab or other anti-integrin molecules in EGIDs.

IgE

Given its role in asthma, allergic rhinitis, and food allergy, IgE would seem to be a logical target in EGIDs; however, clinical trials have not proven this to be the case. In the first trial of omalizumab, an anti-IgE monoclonal antibody, 9 EGE subjects were treated for a total of 16 weeks; 7 of whom had concomitant EoE. Peripheral blood eosinophils and serum free IgE levels decreased throughout the study period as did clinical symptoms, however, there were no significant reductions in gastric or duodenal eosinophilia.⁴⁹ In a subsequent randomized, placebo controlled trial in 30 adults with EoE, omalizumab did not lead to significant reduction in tissue eosinophilia or improvements in clinical symptoms compared to controls.⁵⁰ In a third, unblinded study, 15 pediatric and adult subjects with EoE received omalizumab over a period of 12 weeks. Seven of 15 subjects had significant improvements in clinical symptoms but only 33% achieved histologic resolution as defined by a reduction in peak eosinophil count to <15 eos/hpf and resolution of abnormal endoscopic findings. There was also a significant reduction in esophageal mast cell counts which correlated with improvements in endoscopic findings.⁵¹

The authors concluded that IgE may play a role in a subset of EoE patients for which anti-IgE antibodies could serve as a viable treatment. There are currently no ongoing clinical trials of anti-IgE molecules in EGIDs.

Corticosteroids

Corticosteroids remain the most common medical management option across all EGIDs. Topical, swallowed preparations including viscous budesonide are associated with improved outcomes in EoE while systemic formulations are more commonly used in neEGIDs and are associated with disease remission in small case series.^{2, 48, 53} Several new formulations have been developed for EoE including orodispersible tablets. When compared to viscous budesonide, effervescent budesonide demonstrated similar histologic and endoscopic improvements and was preferred by more than 80% of subjects.⁵⁴ An orodispersible formulation of budesonide is currently approved for EoE in Europe. A phase 2b dose-finding study on fluticasone dissolvable tablets in adults was recently reported. Nearly 70% of treated subjects had ≤ 6 eos/hpf compared to none in the placebo group.⁵⁵

Other agents/targets

Several other molecules hold promise as potential targets for drug development. An antagonist to CRTH2, the eosinophil chemoattractant, has been studied. OC000459 was evaluated in a randomized study of 26 adults with refractory EoE. Over the study period, treated subjects demonstrated significant reductions in esophageal eosinophilia and symptoms of dysphagia compared to controls.⁵⁶ Mast cells have also undergone increasing evaluation as a contributor to EGID pathology. Mast cells are a normal resident throughout GI tissues and play a role in physiologic functions, host defense against infection, and allergic responses. In both

EoE and EG, mast cells can be found in higher numbers in tissue, with increased expression of mast cell genes.^{15, 57-58} Mast cells play a role in eosinophil recruitment to GI tissues and the density of mast cells can correlate with the severity of esophageal eosinophilia. Additionally, mast cell density decreases in response to treatment with resulting improvements in clinical symptoms as shown in studies utilizing anti-IL-5, anti-IgE, and siglec-8 antibodies.^{51, 59-60} Given its role in eosinophil activation and positive feedback on IL-5 and IL-13 production, TSLP may also be a potential target. Tezepelumab, a monoclonal antibody against TSLP, has been studied in asthma with positive results and is currently being investigated in atopic dermatitis. TGF- β could serve as a critical target given its role in long-term remodeling and development of fibrosis. A clinical trial of losartan, an angiotensin-1 receptor antagonist which decreased production of TGF- β in patients with connective tissue disorders and EoE is ongoing. (ClinicalTrials.gov Identifier: NCT03029091) The role of environmental allergies has also been investigated to a limited degree.⁶¹⁻⁶³ EGID patients are typically atopic and frequently have coexisting seasonal or perennial rhinitis, disorders that respond well to subcutaneous immunotherapy (SCIT). In a retrospective study by Robey et al., 10 of nearly 700 patients with EoE were treated with SCIT and no differences in outcomes were noted between those who did and did not receive SCIT.⁶⁴ Epicutaneous immunotherapy (EPIT) which delivers allergen to Langerhan cells in the skin, has been studied in IgE-mediated food allergy, but has also been investigated in EoE. In mice and pig models of EGID, EPIT to peanut can prevent the development of tissue eosinophilia.⁶⁵ In a study by Spergel et al., 20 subjects with milk-triggered EoE were randomized to receive milk EPIT or placebo for 9 months after which milk was reintroduced into the diet. In the intention-to-treat population (all subjects randomized

with at least one application of study treatment), there were no significant difference in mean tissue eosinophil counts compared to placebo, although those in the per protocol population (no change in PPI dose, equivalent milk consumption between screening and end of study) with EPIT had significantly lower peak eosinophil counts than placebo (25.57 ± 31.19 versus 95 ± 63.64).⁶⁶

Conclusion

The field of EGIDs has expanded rapidly over the past two decades with significant gains in understanding disease mechanisms. With these advances have come refined clinical guidelines and standardized outcome measures, and a number of potential therapeutic targets have been identified. The majority of the therapeutics developed are biologics and several have shown significant promise in improving disease outcomes. Combinations of these molecules may help address multiple disease processes at once, although costs may be a limiting factor as would be concerns for higher side effects risks/unintended consequences.⁶⁷ Investigation into immunotherapy has also begun, although more work is needed. The ongoing trials should pave the way for the first FDA-approved medication for EoE/EGIDs and help drive disease modification with prevention of long-term complications.

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Figure 1. Pathophysiology of EoE with Identification of Targets for Drug Development

Exposure to antigen results in activation of T cells and possibly B cells. T cells are polarized to Th2 and further activated through TSLP which then increases the production of IL-4, IL-5, and IL-13. These cytokines promote maturation and activation of eosinophils. Eotaxin-3 and other chemoattractants promote homing to gastrointestinal tissues with binding to mucosal surfaces through siglecs. Once activated release of eosinophil granule content leads to tissue inflammation and barrier damage. CAPN14 and SPINK7 activation decreases production of filaggrin and desmoglein-1, enhancing barrier permeability. TGF-beta is released as a result of tissue inflammation, promoting fibrosis.

CAPN14: calpain 14; CCL26: chemokine (C-C motif) ligand 26; CRTH2: chemoattractant receptor-homologous molecule expressed on Th2 cells; DSG1: desmoglein-1; ECP: eosinophil cationic protein; FLG: filaggrin; IL: Interleukin; MBP: major basic protein; SPINK7: serine peptidase inhibitor, kazal type 7; TGF-beta; transforming growth factor beta; TSLP: thymic stromal lymphopoietin

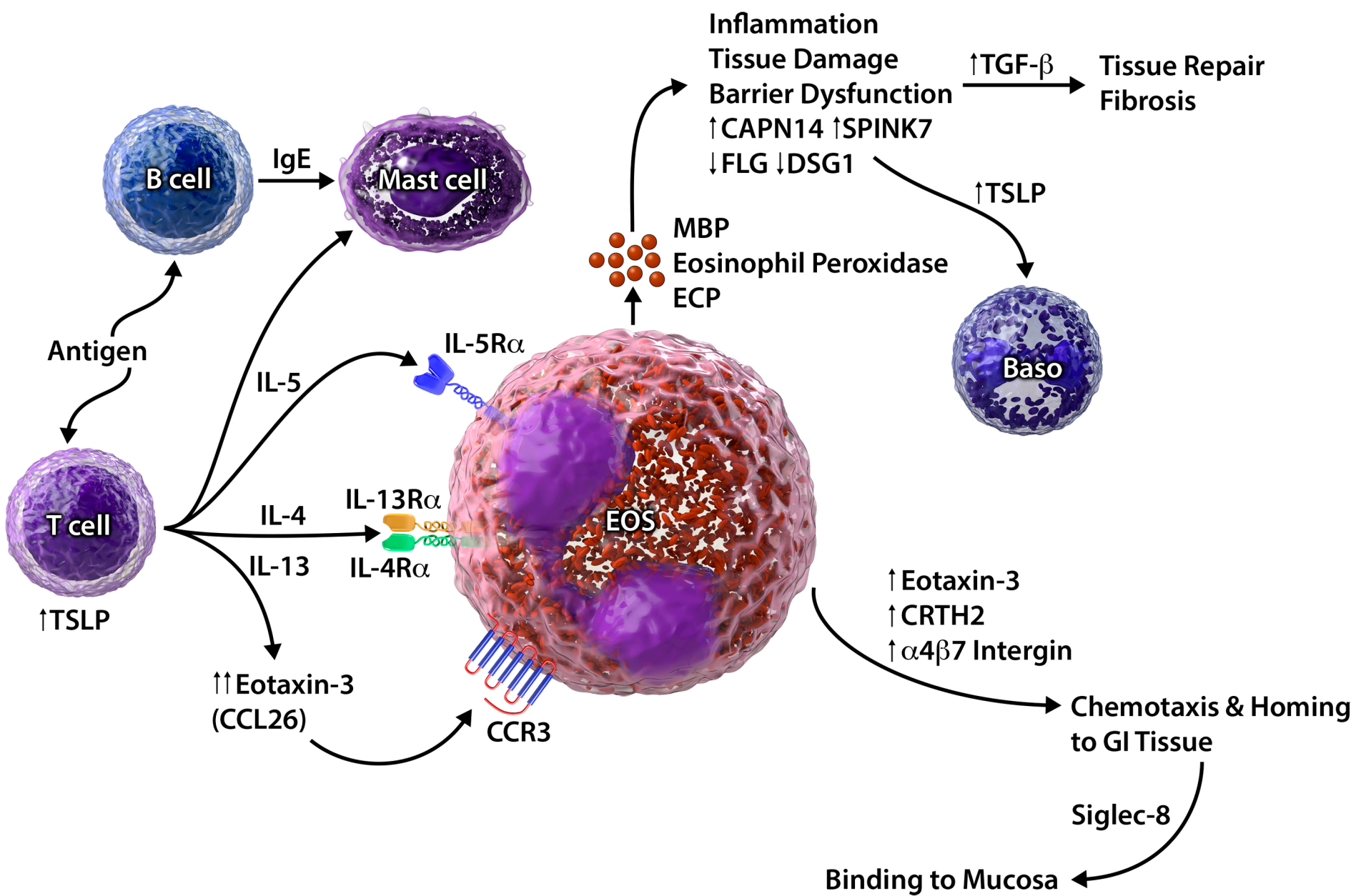
Figure 2: Mechanism of action of biologic therapies in EGID

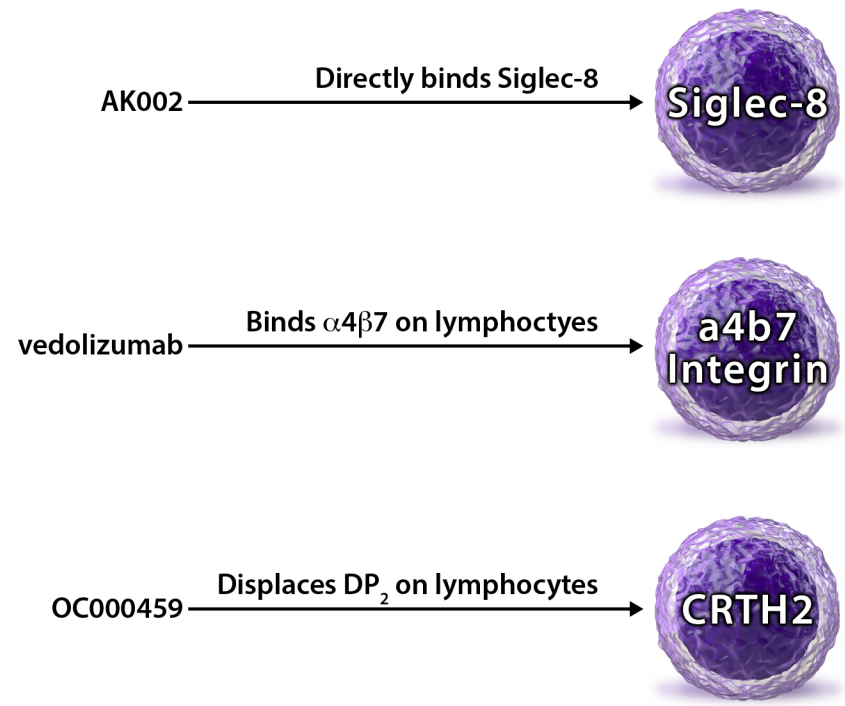
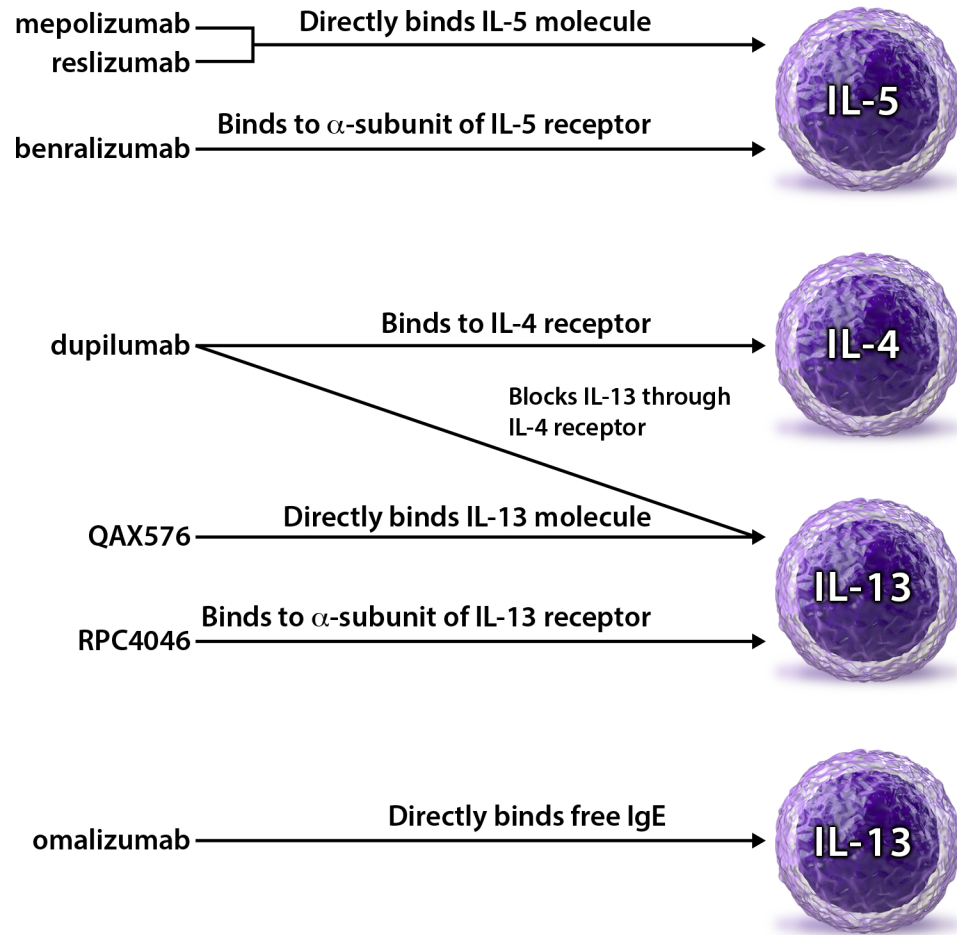
CRTH2: chemoattractant receptor-homologous molecule express on Th2 cells; DP2: D Prostaonoid receptor 2

Table 1. Current status of novel therapeutics in EGIDs

Drug	Past Study/Trial Results	Tissue Eosinophil Response Rate	Current Status
Dupilumab	Improvements in symptoms, endoscopic and histologic findings	Hirano et al. ³² : Mean reduction in peak esophageal eos compared to baseline: 86.8/hpf (placebo: + 14.2%) ≤ 6 eos/hpf: 65% (placebo: 0%) ≤ 15 eos/hpf: 83% (placebo: 0%)	Phase 3 trial (EoE) Phase 2 trial (EG)
QAX576	Reduction in mean esophageal eosinophils	Rothenberg et al. ³³ : Mean reduction in esophageal eos compared to baseline: 60% (placebo: 23.3%)	No ongoing trials
RPC4046	Improvements in symptoms, endoscopic findings, and esophageal eosinophils Benefit in steroid resistant subjects	Hirano et al. ³⁴ : Mean reduction in peak esophageal eos compared to baseline: Placebo: 4.42 ± 59.94 eos/hpf 180mg: 94.76 ± 67.27 eos/hpf 360mg: 99.9 ± 79.53 eos/hpf ≤ 6 eos/hpf: 180mg: 20%, 360mg: 25% (placebo: 0%) ≤ 15 eos/hpf: 50% (placebo: 0%)	No ongoing trials
Mepolizumab	Reduction in esophageal eosinophils, peripheral eosinophils, and mast cells	Stein et al. ³⁵ : Mean reduction in esophageal eos compared to baseline: 8.9-fold Straumann et al. ³⁶ : Reduction in peak esophageal eos compared to baseline: 65% (mean eos: 67%) ≤ 15 eos/hpf: none Assa'ad et al. ³⁷ : ≤ 5 eos/hpf: 8.8% ≤ 20 eos/hpf: 31.6% (peak); 89.5% (mean)	No ongoing trials
Reslizumab	Reduction in esophageal eosinophils; Improvements in symptoms seen in long-term follow-up	Spergel et al. ³⁸ : Mean reduction in peak esophageal eos compared to baseline: Placebo: 24% 1mg/kg: 59%; 2mg/kg: 67%; 3mg/kg: 64%	No ongoing trials
Benralizumab	No trials in EGIDs		Phase 2 trial (EG)
AK002	Reduction in gastric/duodenal eosinophils; Improvement in clinical symptoms; Beneficial in those with both EoE+EG	Dellon et al. ⁴⁴ : Mean reduction in gastric duodenal eos compared to baseline: 92-97% (placebo: +10%) Gastric/duodenal eos ≤ 6 eos/hpf: 95% 0 eos/hpf: 79%	Phase 3 trial(EG/EGE) Phase 2 trial (EoE)
Vedolizumab	Reduction in gastric/duodenal eosinophils in steroid-refractory subjects		No ongoing trials

Omalizumab	No significant decreases in esophageal/gastric/duodenal eosinophils; Improvement in clinical symptoms; Reduction in mast cells	Foroughi et al. ⁴⁹ : Reduction in tissue eosinophils: Duodenum: 59% (median) Gastric: 54-69% Esophagus: + 25% (median) Clayton et al. ⁵⁰ : No significant change in esophageal eosinophils compared to placebo Loizou et al. ⁵¹ : Esophageal eos < 15/hpf: 33%	No ongoing trials
Corticosteroids	Improvements in symptoms, endoscopic findings, and esophageal eosinophils	Various and multiple studies	Budesonide orodispersible - Clinical Use (Europe Only) Fluticasone propionate ODT - Phase 2 trial (EoE)(US)
OC000459	Reductions in esophageal eosinophils and dysphagia	Straumann et al. ⁵⁶ Reduction in esophageal eos: 36.2% (placebo: no change)	No ongoing trials
Tezepelumab	No trials in EGDs		No ongoing trials
Losartan	Trial ongoing/no published results		Phase 2 trial (EoE)
Epicutaneous Immunotherapy (EPIT)	Variable reduction in esophageal eosinophils and symptoms	Spergel et al. ⁶⁶ : Reduction in esophageal eos in per protocol group, but not in intention-to-treat group, compared to placebo	No ongoing trials





Key Messages

- EGIDs are T helper type (Th)2 driven disorders characterized by eosinophilic inflammation of GI tissues, epithelial barrier disruption, and long-term complications including fibrosis
- There are no Food and Drug Administration (FDA) approved medications for Eosinophilic Gastrointestinal Disorders (EGIDs) and current treatment options are limited
- Significant progress has been made in understanding disease mechanisms which has paved the way for development of new treatments
- A variety of treatments are currently being investigated, several of which are in late-phase clinical trials