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REVIEW ARTICLE

Targeted Therapies for Eosinophilic Gastrointestinal Disorders

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Abstract
The growing recognition of eosinophilic gastrointestinal disorders has revealed the limitations of current treatment (mainly based on dietary modification and corticosteroids), and include refractoriness, high recurrence rates, and the need for long-term therapy. Research efforts, mainly in eosinophilic esophagitis (EoE), have unveiled essential pathophysiological mechanisms leading to these disorders, which bear some similarities to those of atopic manifestations and are shared by eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC). Novel targeted therapies, some imported from bronchial asthma and atopic dermatitis, are currently being assessed in EoE. The most promising are monoclonal antibodies, including those targeting interleukin (IL)-13 (cendakimab) and IL-4 (dupilumab), with phase 3 trials currently ongoing. The potential of anti-integrin therapy (vedolizumab) and Siglec-8 blockers (antolimab) in EGE are also promising. Non-biological therapies for eosinophilic gut disorders, which include preventing the activation of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) and chemoattractant receptor expressed on T helper 2 cells (CRTH2) signaling pathways, and other potential targets that deserve investigation in eosinophilic gut disorders, are reviewed.

1 Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are chronic, eosinophil-rich inflammatory primary disorders of the gastrointestinal tract that are not related to infection, medication, or inflammatory bowel disease (IBD) [1]. EGIDs present diverse symptomatology, mainly dependant on the sections of the digestive tract affected (esophagus to rectum) and on the depth of the inflammation in the intestinal wall, from the mucosa to the serosa [2]. Thus, eosinophilic esophagitis (EoE), the most prevalent and best known form of EGID, is a chronic condition characterized by infiltration of the esophageal mucosa by ≥ 15 eosinophils per high-power field (eos/hpf), which manifests in esophageal dysfunction: mainly dysphagia and food impaction. Eosinophilic gastritis (EG) causes abdominal pain, vomiting, and failure to gain weight [3]. Eosinophilic gastroenteritis (EGE)

Key Points

Eosinophilic gastrointestinal disorders are primary T helper 2-driven disorders with expansive epidemiology characterized by eosinophilic inflammation of gastrointestinal tissues and varied symptoms, depending on the sections of the digestive tract affected and on the depth of the inflammation in the intestinal wall

Current therapies mainly based on avoiding food antigens and corticosteroids may relieve symptoms and eosinophilic inflammation in the short term, but a proportion of patients are refractory. Advances made in the last few years in understanding cellular and molecular pathways paved the way to develop new targeted therapies

A variety of treatments are currently being investigated, several of which are in late-phase clinical trials—monoclonal antibodies targeting interleukin (IL)-13, IL-4, and the α subunit of the IL-5 receptor (IL-5Rα) and Siglec-8 blockers being the most promising therapies to be incorporated into clinical practice

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typically involves the stomach and small bowel, producing a variety of symptoms in both the upper and lower digestive tract [4]. Finally, eosinophilic colitis (EC), the infiltration of eosinophils throughout the colon, typically presents with abdominal pain and diarrhea [5]. Table 1 classifies primary EGID and causes of secondary gut eosinophilia.

EGID has been known of as early as 1937 when Kaijser first described EGE [6], but interest has only grown recently, after expanding recognition [7] and the growing prevalence of EoE, its most common representative, with a current prevalence of around 63 cases per 100,000 inhabitants [8] in Westernized countries. As most of the accumulated knowledge from non-esophageal EGID comes from case reports and short case series, systematized estimations on its epidemiology are scarce. A 2010 American electronic survey estimated an overall prevalence for EGE or colitis of 28 per 100,000 [9]; this figure has recently been corrected, after a large health plan claims database provided USA prevalence rates for EG, EGE, and EC of 6.7, 8.2, and 3.5 cases/100,000 inhabitants, respectively [10].

Growing evidence supports the role of food allergens and T helper (Th)2-driven cytokines in the pathogenesis of EGID [11]; positive skin testing or specific immunoglobin E (IgE) levels to food allergens are common in children and adults with EGID, and are associated with several atopic diseases [11–13]. As in other allergies, inflamed tissues in EGID contain abundant mast cells and basophils [14–17]. In addition, inherited and autoimmune connective tissue disorders have been shown to be associated with EoE [18] and other EGID [19] by involving mutations in genes encoding for components of the extracellular matrix, or signaling molecules that results in an impaired epithelial barrier function and increased uptake of antigens [20, 21].

Table 1 Classification of eosinophil-associated gut disorders

Primary eosinophilic gastrointestinal disorders
Eosinophilic esophagitis
Eosinophilic gastritis
Eosinophilic gastroenteritis
Eosinophilic colitis
Hypereosinophilic syndrome with gastrointestinal involvement
Diseases with secondary gastrointestinal tract eosinophilic infiltration
Parasitic infection
Hypersensitivity to food or drugs
Inflammatory bowel disease
Gastroesophageal reflux disease
Esophageal atresia
Connective tissue disorders
Vasculitis
Pemphigoid
Neoplasia
Achalasia
Graft-versus-host disease

Significant advances have been made in the last decade to characterize cellular and molecular pathways underlying primary EGID [14, 22] to define diagnostic criteria and standardize treatment approaches [23, 24] and to identify potential treatment targets. Searches in the PubMed and Scopus libraries were performed, and the ClinicalTrials.gov database was consulted; treatment studies and clinical trials in EGIDs were included in this review.

This article provides a state-of-the-art review on biological-based and novel pharmacological strategies aimed at targeting eosinophilic inflammation in EoE and non-esophageal EGID currently under investigation and others pending.

2 Goals for Treatment in EGID and Limitations in Assessing Its Effectiveness

Treatment endpoints in EGID should ideally include complete resolution of symptoms, histological inflammation and endoscopic findings (mucosal healing), and prevention of remodeling and related complications [25, 36]. Further therapeutic targets should also involve avoiding side effects of drugs and long-term diets, maintaining a proper nutritional status, correcting feeding dysfunction, restoring social activities, and increasing quality of life (QoL). However, assessing these goals is somehow conflictive, as revealed in patients with EoE, where symptoms consistently showed poor correlation with eosinophil density in esophageal biopsies [27]. In fact, symptomatic improvement is insufficient and does not always reflect changes in disease activity. Younger patients may not be able to fully describe their symptoms, which are not the same as those for adolescents and adults. Dysphagia depends not only on the existence of esophageal caliber abnormalities or active mucosal inflammation, but also on the consistency of the food ingested and the patient's behavioral adaptations. Disease-specific instruments that are being currently applied in trials quantify not only symptoms, but also the difficulties foreseen by patients with respect to eating food of different consistencies and dietary or behavioral modifications for specific foods [28, 29]. As for non-esophageal EGID, the nonspecific nature of most symptoms hindering this diagnosis is considered by physicians before endoscopy [30].

With the exception of EoE, definitions that are validated and agreed on for most EGID in terms of eosinophil densities, additional histological findings, and symptoms are lacking [31]. Providing validated definitions for symptomatic, histological, and, for EoE, endoscopic remission constitutes a major challenge in EGID therapy. Eosinophils are part of the normal histology of all segments of the digestive tract

except in the esophagus; therefore, defining criteria for histological remission is conflictive. For EoE, it has been defined that a cutpoint of < 15 eos/hpf after treatment appropriately identified patients with symptom and endoscopic improvements in regular clinical practice [32], but stringent histological thresholds < 6 eos/hpf are generally required in trials assessing new drugs. The EoE Histology Scoring System (EoEHSS) evaluates additional histological findings by scoring eight individual histological features [26], which potentially overcomes the limitation of assessing eosinophil counts alone [33].

Profibrogenic mediators contained in eosinophil granules are responsible for fibrous remodeling in EGID leading to fold thickening, strictures [34], and, in the case of EoE, narrow-caliber esophagus [35], detectable through radiology and endoscopy. The EREFS (edema, rings, exudates, furrows, and strictures) scoring system grades the five major esophageal endoscopic features in EoE [36]; the improvement of inflammatory and fibrotic features especially is now an objective of EoE treatment, and the last does not necessarily accompany histological remission. This may be due to the delay in resolution of fibrosis, which can take many months to soften.

3 Current Therapeutic Options and Unmet Medical Needs for EGID

As EGID primarily involves food allergy, dietary therapy is a common treatment option. Elimination or avoidance of specific foods provides disease resolution in a significant proportion of patients [37–39]. Exclusive feeding with elemental diets and empirically eliminating the most common foods potentially involved in triggering and maintaining the disease provides the best results, as avoiding foods patients are sensitized to is inefficient, as patients are frequently sensitized to many allergens [7]. Patients who do not respond to diets and those who do not tolerate restrictive diets or must avoid multiple foods should consider drug-based treatments.

Proton-pump inhibitors (PPIs) lead to reductions in eosinophilic infiltration and symptoms in 50% of pediatric and adult patients with EoE [40]. Beyond their blocking effect of gastric acid secretion, PPIs have an intrinsic anti-inflammatory effect, by downregulating the esophageal gene expression of eosinophil chemoattractant C–C Motif Chemokine Ligand 26 (*CCL26* or *eotaxin-3*) Th2 cytokines interleukin (*IL*)*-5* and *IL-13* similarly to topical steroids [41]. An explanation for this anti-inflammatory effect has been provided by demonstrating that omeprazole prevented the binding of signal transducer and activator of transcription 6 (STAT6) transcription factor to the promoter region of the *eostaxin-3* gene in vitro, thus avoiding its transcription [42]. However, corticosteroids are, by far, the most widely used drugs to treat EGID in patients of all ages [7, 23]. Orally administered systemic steroids constituted the initial therapy for these disorders; dosages of 0.5–1 mg/kg/day of prednisone were highly effective in reducing eosinophilic tissue inflammation and blood eosinophilia as well as improving symptoms in patients with non-esophageal EGID [7, 43]. After an initial treatment period of 7–10 days, the dose was tapered until it was withdrawn after a few months. However, some patients are steroid dependent [44] and will need to resume previous doses, maintain remission by using low doses, substitute prednisone for budesonide [2, 45, 46], or try other alternatives. In the particular case of EoE, systemic steroids offer no advantage over topical fluticasone formulas [47].

Three different evolutionary patterns have been described to characterize the natural history of EGE: a single outbreak of symptoms lasting < 3 months; a recurrent pattern of disease, with flare-ups during extremely variable intervals; and a continuous course with persistent symptoms [48]. Contrarily, EoE is considered a chronic disease where, in the absence of treatment, inflammation and symptoms tend to persist; thus, patients will require long-term maintenance therapy with budesonide or fluticasone [49, 50] because drug withdrawal is likely to induce a rapid recurrence of the inflammation. Steroid-sparing therapies are required, despite both medications being considered safe when used long term, and no significant risk of adrenal suppression has been described yet. Non-responsive patients to steroids have also been described [7, 51].

Even when effective, current diets and drug-based therapies for EGID are disease-modifying treatments, and long-term adherence is required; there is no evidence that patients under dietary therapy will outgrow their disease food triggers. PPI therapy for EoE is generally considered safe, but recent concerns on the potential complications with long-term use have arisen [52, 53]. One-quarter of responder patients will need double doses of PPI to maintain sustained remission in the long term [54]. As a result, new drugs have been developed to respond to unmet medical needs, most of them imported from other Th2-mediated allergic diseases. Table 2 summarizes novel treatments that are being investigated, several in late-phase randomized clinical trials (RCTs).

4 Identifying Targets for Treatment in EGID

Significant advances from research in EoE during the last decade have helped provide a plausible pathophysiological hypothesis that integrates exposure to antigens and environmental modifiers and genetics with clinical and histopathological features of the disease [22], producing an explanatory model for the whole EGID.

The gastrointestinal epithelium represents an immunologically active surface that initiates and perpetuates inflammatory and structural changes that characterize EGID. The activation of epithelial and dendritic cells after exposure (or lack of exposure) to components of the gut lumen (i.e., bacteria and food antigens) induce the expression of homing and retention molecules for immune cells, such as invariant natural killer T (iNKT) cells [55, 56]. iNKT cells are a major source of Th2 cytokines, including IL-13, which directly induce changes in gene expression patterns on epithelial cells and lead to thymic stromal lymphopoietin (TSLP) secretion. TSLP further promotes secretion of IL-13, IL-4, and IL-5 by acting on Th2 cells, which can potentially be blocked by antibodies directed to the soluble cytokine or its receptor, or by interfering with its signaling pathways, which transmit extracellular information to the cell nucleus.

IL-5 promotes differentiation, maturation, and release of eosinophils from the bone marrow through STAT5, while IL-13, primarily acting together with IL-4 through STAT6, promotes the transcription of *calpain-14* and *SPINK7* genes, as well as codifying for the *CCL26*/*eotaxin-3* gene. While the former contribute to disrupting the epithelial surface to increase its permeability by downregulating *desmoglein 1* (*DSG1*) expression, among other tight junction and desmosome proteins [57, 58], CCL26 acts as a potent chemoattractant for eosinophils and mast cells [59]. In fact, mast cell density is also increased in EGID [14, 16, 17, 60] regardless of atopic background, and is reduced to normal after treatment. A correlation between symptom score and expression level of mast cell proteases in mucosal biopsies is found in patients with EoE [16].

The chemoattractant receptor expressed on Th2 cells (CRTH2) also plays an important role in chemotaxis of eosinophils. Th2 cytokines also trigger the production of IgE by plasma cells.

In addition to the epithelium, activated eosinophils also contribute to regulate the inflammation of gastrointestinal tissues. Eosinophils release vascular adhesion molecule 1 (VCAM-1) and vascular endothelial growth factor (VEGF) from their granules, which are responsible for angiogenesis and endothelial activation, and are essential in directing inflammatory cells towards intestinal tissues [22]. Sialic acid-binding immunoglobulin-type lectins (Siglecs) help eosinophils bind to the cell surface [61].

Eosinophils also contribute to motor disturbances that appear in EGIDs through transforming growth factor-β1 (TGF-β1) and major basic protein or MBP, which lead to hyperplasia and hypercontractility of smooth muscle fibers in the digestive tract wall [62]. In addition, when acting in a paracrine environment characterized by the presence of Th2 cytokines and eotaxins, eosinophils regulate the process of epithelial-mesenchymal transition, which favors the activity and proliferation of fibroblasts and the subsequent synthesis of extracellular matrix components. A variety of novel therapies aiming to modify these processes, restore the integrity of the mucosal barrier, reduce tissue eosinophilia and derived changes, and improve clinical outcomes are being developed.

5 Monoclonal Antibodies

Biological agents are an essential therapy for inflammatory autoimmune diseases, which include several intestinal, skin, and articular entities, and have become a first-line option for a variety of malignancies. In recent years, the use of monoclonal antibodies was expanded to atopy, especially allergic and eosinophilic airway inflammation, common to most asthma patients [63]. This expansion extended to EGID, with their use in EoE as early as in 2008, when the anti-tumor necrosis factor-α (anti-TNF-α) antibody infliximab was used in a short series of three adults with severe disease; after two infusions, no changes were noted in eosinophilic tissue infiltration or symptoms [64]. Despite TNF-α being upregulated in esophageal EoE patient biopsies [66], Th2 cell-mediated responses are mainly involved in EGID [67, 68]; therefore, recent research has focused on blocking their molecular pathways.

5.1 Targeting the IL-5 Pathway for Reducing Gut Infiltration by Eosinophils

Binding of IL-5 to the α subunit of the IL-5 receptor (IL-5Rα) promotes the heterodimerization of IL-5Rα and βc subunits. As a consequence, many signal transduction pathways are activated, including Janus kinase (JAK)/STAT modules, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), among others [68]. The combined stimulation of these kinases and transcription factors drives the expression of key genes responsible for differentiation, survival, degranulation, adhesion, and recruitment of eosinophils [69]. Esophageal biopsies from patients with active EoE show upregulated *IL-5* gene and its protein [41], and blood-circulating lymphocytes of these patients produce high amounts of IL-5, which correlates with the severity of esophageal tissue eosinophilia [70]. The high specificity of monoclonal antibodies targeting either the circulating cytokine or its membrane receptors on eosinophils and its involvement in the majority of eosinophilic conditions [68] made it an attractive target for treatment of EGID.

Three anti-IL-5 pathway monoclonal antibodies have been developed and investigated in EGID. Mepolizumab and reslizumab bind to and neutralize soluble IL-5, thereby interfering with its ligation to IL-5Rα. Benralizumab is directed against the membrane-expressed IL-5Rα chain over eosinophils, hindering the access of IL-5 to its receptor and inducing

Table 2 Randomized clinical trials evaluating monoclonal antibodies for the treatment of eosinophilic gastrointestinal disorders

Study	Target	Indication	Monoclonal antibody	Mechanism of action	Design	Population (sample size)	Dosage	Histological response	Clinical response	Tolerability
Straumann et al. 2010 [73]	IL-5	EoE	Mepolizumab	Binds IL-5	Placebo-controlled, phase 2 RCT	Adults (11)	Two infusions of 750 mg active drug or placebo weekly. Two more infusions of 1500 mg active drug or placebo in case of no histological response	No patient achieved histological remission. 54% reduction in mean eosinophil count in mepolizumab group vs. 5% reduction in placebo group	No significant differences in symptom improvement compared to placebo	Few mild AEs; none related to active drug
Assa'ad et al. 2011 [74]	IL-5	EoE	Mepolizumab	Binds IL-5	Placebo-controlled, phase 2 RCT	Children (59)	Three infusion of 0.55, 2.5, or 10 mg/kg monthly	8.8% of patients achieved histological remission (< 5 eos/hpf). 89.5% of patients achieved < 20 eos/hpf. Better results with the highest dose	No significant improvement in symptoms	No related AE
Spergel et al. 2012 [76]	IL-5	EoE	Reslizumab	Binds IL-5	Placebo-controlled, phase 2 RCT	Children (227)	Four infusions of 1, 2, or 3 mg/kg monthly or placebo	Peak eosinophil counts reduced by 59%, 67%, and 64%, in the 1, 2, and 3 mg/kg groups, respectively vs. 24% for placebo. Most patients had > 5 eos/hpf at end of treatment	Non-significant improvements in symptoms were observed in all treatment groups, which were not associated with changes in esophageal eosinophil counts	Well tolerated, headache and cough being the most common AEs
Clayton et al. 2014 [107]	IgE	EoE	Omalizumab	Binds free IgE	Placebo-controlled, phase 2 RCT	Adolescents and adults (30)	0.016 mg/kg/IgE every 2–4 weeks, depending on body weight, for 12 weeks	33% achieved peak eosinophil count < 15 eos/hpf. More effective in children than in adults	Some clinical improvement: 47%. Clinical remission in 1/3 patients	No serious AE; high drop out because of lack of efficacy

Table 2 (continued)

Study	Target	Indication	Monoclonal antibody	Mechanism of action	Design	Population (sample size)	Dosage	Histological response	Clinical response	Tolerability
Rothenberg et al. 2015 [87]	IL-13	EoE	Dectrekumab (QAX576)	Binds IL-13	Placebo-controlled, phase 2 RCT	Adults (23)	Three infusion of active drug 6 mg/kg monthly or placebo	Peak eosinophil count decreased by 60% in the active group but increased in the placebo group No benefit to achieved > 75% reduction in esophageal eosinophil counts compared to placebo	QAX576 showed a non-significant trend to symptomatic improvement	Mild AE: cough and GERD symptoms
Hirano et al. 2019 [88]	IL-13	EoE	Cendakimab (RPC4046)	Binds IL-13	Placebo-controlled, phase 2 RCT	Adults (99)	180 mg, 360 mg, or placebo weekly for 16 weeks	50% of patients in both active arms had < 15 eos/hpf after treatment (0% in the placebo arm). 25% of patients in the 180 mg RPC4046 group and 20% in the 360 mg RPC4046 group had < 6 eos/hpf after treatment	The 360 mg group showed a non-significant reduction in symptoms	No serious AE
Hirano et al. 2020 [94]	IL-4/IL-13	EoE	Dupilumab	Binds the α-subunit of the IL-4 receptor (inhibits IL-13 receptor)	Placebo-controlled, phase 2 RCT	Adults (47)	300 mg or placebo weekly for 12 weeks	Peak eosinophil count reduced by 91.8% in the dupilumab arm vs 15.1% increase in the placebo arm. 82.6% of patients treated with dupilumab achieved < 15 eos/hpf. 65.2% of patients treated with dupilumab achieved < 6 eos/hpf	Symptom score (as measured with the Straumann's dysphagia instrument) reduced significantly in patients treated with dupilumab	No serious AE

Table 2 (continued)

Study	Target	Indication	Monoclonal antibody	Mechanism of action	Design	Population (sample size)	Dosage	Histological response	Clinical response	Tolerability
Dellon et al. 2019 [98]	Anti-Siglec-8	EG and EGE	Antolimab (AK002)	Induces apoptosis of activated eosinophils and inhibits mast cell activation	Placebo-controlled, phase 2 RCT	Adults (59)	AK002 0.3–1.0 mg/kg, AK002 0.3–3.0 mg/kg, or placebo for 12 weeks	Mean eosinophil count in gastric and duodenal biopsies reduced by 92–97% from baseline in AK002 arms vs 10% in the placebo arm. Overall, 95% of patients allocated to AK002 had < 6 eos/hpf and 79% had 0 eos/hpf	AK002 reduced symptom score > 30% from baseline in 69% of patients vs 5% of placebo	Mild to moderate infusion-related reactions after the first infusion

AE adverse events, *EG* eosinophilic gastritis, *EGE* eosinophilic gastroenteritis, *EoE* eosinophilic esophagitis, *GERD* gastroesophageal reflux disease, *IgE* immunoglobin E, *IL* interleukin, *RCT* randomized controlled trial, *eos/hpf* eosinophils per high-power field

eosinophil target-cell depletion through natural killer cell-mediated antibody-dependent cellular cytotoxicity [69].

5.1.1 Mepolizumab

After demonstrating effectiveness as a steroid-sparing agent in idiopathic hypereosinophilic syndrome [71], mepolizumab was initially assessed in three adults with severe EoE [71]. After three infusions, symptoms, QoL, and endoscopic features of EoE improved and esophageal eosinophil counts reduced (although eosinophil density remained above 20 cells/hpf). Two double-blind RCTs of mepolizumab in adults [72] and children [73] with EoE were thus designed.

In the first trial, 11 adults with active disease were randomized to receive two weekly infusions of 750 mg of mepolizumab ($n = 5$) or placebo ($n = 6$). Biopsies performed 2 weeks later showed a 54% reduction in mean eosinophil count only in mepolizumab-treated patients, but none of them achieved the primary endpoint of < 5 eos/hpf. Eosinophil count did not show further improvement after two additional infusions of 1500 mg of mepolizumab or placebo administered at 4-week intervals [73] (no dose response was demonstrated after the maximal histological response was achieved); endoscopic findings and symptoms did not significantly improve compared to placebo.

The pediatric trial randomized 59 children to receive mepolizumab infusions of 0.55, 2.5, or 10 mg/kg every 4 weeks, without a placebo group [74]. After 12 weeks, histological assessment showed a significant reduction in epithelial eosinophil counts, but only five out of the 57 patients who provided endoscopic biopsy samples (8.8%) achieved < 5 eos/hpf. No significant changes in symptoms during therapy were noted. A second biopsy performed at week 24, with no additional mepolizumab doses, showed increases in esophageal eosinophilia in all treatment arms.

5.1.2 Reslizumab

This monoclonal antibody was approved by the Food and Drug Administration (FDA) in 2016 as an add-on maintenance treatment for adults with severe eosinophilic asthma [75], with dosing based on patient weight at 3 mg/kg once every 4 weeks via intravenous infusion. The effect of reslizumab on EGID has been exclusively assessed in children and adolescents with EoE; 227 patients were randomly assigned to receive four intravenous infusions of 1, 2, or 3 mg/kg of reslizumab or placebo every 4 weeks. All treatment groups, including placebo, showed improvements in physician global assessment scores and reductions in eosinophil counts at the end of the trial, with no statistically significant differences between reslizumab and placebo groups. Only 4.4% of patients achieved complete histological remission, defined as < 5 eos/hpf [76].

One potential explanation for the poor results of anti-IL-5 therapies for EoE is the short treatment length; three to four doses could be insufficient to reverse inflammatory changes [76] and to act on fibrous remodeling and derived symptom burden [68]. However, the open-label extension of this trial for up to 9 years has recently shown that tissue eosinophil counts improved during extended therapy [77].

5.1.3 Benralizumab

Benralizumab blocks the IL-5Rα subunit of the IL-5 receptor and thereby recognizes (and binds) eosinophils directly. Afucosylation of this antibody improves its affinity for the FcγRIIIa receptor on natural killer cells, enhancing the ability of benralizumab to destroy IL-5Rα-expressing cells, independent of their relative dependency on IL-5 or other mediators for their growth or survival, even in cases of low-level expression of the IL-5Rα chain [78]. As a result, benralizumab depletes peripheral blood eosinophils rapidly and pronouncedly [69] and its efficacy, contrary to anti-IL-5 antibodies, is not decreased in the presence of high-level IL-5 production. As an additional advantage, again contrary to anti-IL-5 antibodies, the pharmacokinetics of benralizumab show a linear relationship between drug dosing and concentration.

Benralizumab has been approved exclusively to treat eosinophilic asthma in adolescents and adults after demonstrating superior effectiveness compared to IL-5 blockers [79]. Bone marrow eosinophils in asthmatic patients treated with a single intravenous (1 mg/kg) or 3 monthly subcutaneous (100 mg) doses of benralizumab were completely suppressed after 4 weeks dosing [80], and lung eosinophils reduced by 90% [81]. An ongoing placebo-controlled RCT (NCT03473977) is currently investigating the efficacy and safety of benralizumab in EG and EGE.

5.2 The Role of the IL-13 Pathway in Pathophysiology and Therapy of Eosinophilic Gut Disorders

IL-13 is involved in several eosinophilic inflammatory disorders, such as bronchial asthma and atopic dermatitis, where the anti-IL-13 antibody tralokinumab is clinically beneficial [82, 83]. In EoE, IL-13 also plays a central role, as it is essential for eosinophil recruitment and epithelial dysfunction; the *IL-13* messenger RNA (mRNA) is upregulated in esophageal biopsies from EoE patients [66] and esophageal cell cultures stimulated with IL-13 reproduce the EoE-specific transcriptome [84] and secrete eotaxin-1/CCL11 and eotaxin-3/CCL26, responsible for eosinophil recruitment and accumulation [85]. IL-13 also downregulates gene expression of desmosome proteins, basement membrane components, and adhesion molecules, thus increasing epithelial permeability [22], and it also has been involved in esophageal remodeling by enhancing collagen deposition [86]. Therefore, preventing the effects of IL-13 by blocking it with monoclonal antibodies is proposed to effectively control EoE-related features. Two phase 2 RCTs have already investigated monoclonal antibodies targeting IL-13 (QAX576 and RPC4046) in patients with EoE.

5.2.1 Dectrekumab (QAX576)

After being studied in pulmonary fibrosis, dectrekumab was the first anti-IL-13 monoclonal antibody used to treat patients with EGID assessed in an RCT [87] with the primary endpoint of a greater than 75% decrease in peak eosinophil counts at week 12. Overall, 23 adults with EoE were randomly assigned to receive three intravenous infusions of dectrekumab (6 mg/kg) or placebo every 28 days, with a 6-month follow-up. Patients treated with the active drug decreased their mean count at week 12 by 60%, with no patient achieving histological remission and no significant advantage over placebo. However, patients who received dectrekumab showed a non-significant trend toward improvement in dysphagia severity, as measured with the Mayo Dysphagia Questionnaire. Despite these negative results, dectrekumab normalized the expression levels of some EoE-related genes, with changes differing between responders and nonresponders to the drug. The development of this drug in EoE has since been discontinued.

5.2.2 Cendakimab (RPC4046)

This antibody blocks IL-13 and prevents its binding to the receptor subunits α1 (IL-13Rα1) and 2 (IL-13Rα2). A dose ranging study of cendakimab in EoE has been developed to assess its efficacy to reduce mean eosinophilic count in esophageal biopsies as the primary outcome [88]. Ninety-nine adults with EoE were randomly allocated to receive either a 10-mg/kg intravenous loading dose of cendakimab followed by 360 mg subcutaneously once a week, a 5-mg/kg intravenous loading dose plus 180 mg subcutaneously once a week, or placebo for 16 weeks in a 1:1:1 ratio. Both groups of patients allocated to cendakimab exhibited statically significant reductions in mean eosinophil counts compared to placebo. Regarding the rate of patients achieving histological remission, 50% of patients treated with 180 mg and 360 mg had < 15 peak eos/hpf compared with 0% placebo, and 25% of patients in the 180-mg RPC4046 group and 20% in the 360-mg RPC4046 group had < 6 peak eos/hpf after treatment.

Secondary efficacy outcomes consisted of improvements in esophageal endoscopic and histological severity features and symptom frequency and severity. Despite endoscopic

EREFS and histological EoEHSS scores improving significantly for both doses of cendakimab compared to placebo, a non-significant trend to symptomatic improvement in favor of patients treated with active medication was only demonstrated. Of note, subgroup analyses found greater symptom improvement in patients whose disease was identified as steroid refractory.

A 52-week, open-label, extension trial of cendakimab has provided results just recently. A sustained symptomatic and histological improvement following successful induction therapy among patients treated with the 360-mg dose was observed [89]. Evaluating the effectiveness of cendakimab to maintain remission of EoE in the long term is required.

5.3 Blocking IL-4 Receptor: An Improved Mechanism

IL-14 and IL-13 are closely related Th2 cytokines, sharing 30% of their sequences. Contrary to IL-13, IL-14 is not upregulated in the esophageal epithelium of patients with EoE compared to healthy controls [90]. The binding of IL-4 and IL-13 to a common heterodimeric receptor (IL-4Rα and IL-13Rα1) produces overlapping downstream effects [91]; therefore, separately blocking IL-4 and IL-13 is not completely effective.

5.3.1 Dupilumab

After being approved to treat asthma [92] and atopic dermatitis [93], this monoclonal antibody directed against the IL-4 receptor α subunit (IL-4Rα) which simultaneously blocks the signaling pathways of IL-4 and IL-13, is now being assessed in EoE. A phase 2, double-blind, placebo-controlled RCT completed in 2017 has been recently published [94]. The primary endpoint was improvement in dysphagia as measured from baseline to week 10 with the Straumann's Dysphagia Symptoms score. Reductions in peak esophageal intraepithelial eosinophil count and EoE histological scores and improvements in esophageal endoscopic features constituted secondary outcomes. Overall, 47 adult patients with moderate-to-severe EoE were randomly allocated to receive dupilumab (600-mg loading dose followed by 300 mg weekly) or placebo for 12 weeks. At week 10, a significant improvement in the ability to swallow was reported by patients who received dupilumab compared to placebo (45% vs. 19% improvement from baseline in the Straumann's Dysphagia Symptoms score; $p < 0.05$). In addition, 82.6% of patients treated with dupilumab achieved reductions in peak eosinophil counts below 15 eos/hpf and 65.2% had less than 6 eos/hpf. Endoscopic and histological activity scores, as measured by EREFS and EoEHSS scores, improved significantly among treated patients, and endoFLIP-measured esophageal compliance increased accordingly.

A currently ongoing phase 3 RCT is assessing long-term efficacy and tolerability of dupilumab 300 mg every week or every 2 weeks compared to placebo in adults and adolescents with EoE (NCT03633617).

Dupilumab is also being investigated for use in EG and EGE in a phase 2 trial (NCT03678545). Subjects will receive 600 mg once followed by 300 mg doses of dupilumab or placebo every 2 weeks for a total of six injections, followed by an open-label phase in the case of response.

Table 3 summarizes ongoing trials with novel biological agents in EGID.

5.4 Promoting Apoptosis of Eosinophils: A Novel and Promising Treatment for EGID

Siglecs are found on the membrane of eosinophils and other immune cells, where they play a role in cell signaling and immune system regulation. Human eosinophils, basophils, and mast cells preferentially express Siglec-8 [95], which is involved in eosinophil apoptosis and clearance, inhibition of mast cell-released mediators, and reversal of tissue remodeling. The potential of two anti-Siglec-8 antibodies, AK001 and AK002, is currently being assessed in nasal polyposis, systemic mastocytosis, and keratoconjunctivitis (NCT02734849, NCT02808793, and NCT03379311).

The administration of anti-Siglec-8 monoclonal antibodies to murine models of EGE has significantly reduced eosinophils and mast cells in the stomach, small intestine, and mesenteric lymph nodes, and decreased levels of inflammatory mediators [96]; another mouse EoE model achieved the same on esophageal, blood, and bone marrow eosinophils [97].

The ENIGMA trial, a randomized, phase 2, placebo-controlled study aiming to assess the efficacy of the anti-Siglec-8 antibody antolimab (AK002) in adult patients with EG and/or EGE has recently been completed [98]. Fifty-nine patients were randomized to AK002 (low dose 0.3–1.0 mg/kg or high dose 0.3–3.0 mg/kg) or placebo for 3 months. The primary endpoint consisted of mean percentage change in eos/hpf counts in gastric and/or duodenal biopsies from baseline; the secondary endpoint was the proportion of patients with symptomatic plus histological response (defined as both a > 75% decrease in tissue eosinophilia and a > 30% improvement in symptoms assessed by a specifically designed patient-reported outcome questionnaire). Compared to values at baseline, antolimab groups had an overall 95% mean reduction of tissue eosinophilia, which increased by 10% in patients allocated to placebo. Overall, 69% of patients treated with antolimab experienced clinic-histological response, compared to 5% of placebo patients; no significant differences in efficacy between low and high doses of antolimab were noted. An ongoing open-label extension will confirm the safety and tolerability of

Table 3 Ongoing trials with novel therapies for eosinophilic gastrointestinal disorders

Study drug	ClinicalTrials.gov ID	Target	Mechanism of action	Indication	Design	Dosage	Primary endpoint
Benralizumab	NCT03473977	IL-5Rα	Recognizes and binds eosinophils preventing the effect of IL-5	EG or EGE	Placebo-controlled, phase 2–3 RCT	3 monthly subcutaneous doses of 30 mg or placebo	Induction of disease remission, defined by the percentage of patients that achieve histological remission in the stomach, peak eosinophil counts < 30/hpf, compared to placebo
Dupilumab	NCT03633617	IL-4Rα	Blocks downstream activation pathways of IL-4 and IL-13	EoE	Placebo-controlled, phase 3 RCT	Subcutaneous dupilumab 300 mg doses every week or every 2 weeks or placebo	Proportion of patients achieving ≤ 6 eos/hpf peak esophageal intraepithelial eosinophil count of eosinophils at week 24, and absolute change in Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24
Dupilumab	NCT03678545	IL-4Rα	Blocks downstream activation pathways of IL-4 and IL-13	EG or EGE	Placebo-controlled, phase 2 RCT	Subcutaneous injection every 2 weeks as follows: 600 mg initial dose, and 300 mg subsequent doses for a total of 6 injections, or placebo	Mean change in peak eosinophil counts in the 5 most eosinophil dense hpfs in the gastric mucosa, compared to placebo at week 12
Losartan potassium	NCT03029091	TGF-β	The synthesis of TGF-β1, which promotes fibrosis, can be inhibited by losartan	EoE	Open-label study (all participants receive the study medicine)	Study drug doses increase depending on weight and tolerance, up to 100 mg per day, orally	Change in peak esophageal eosinophil count after 4 months of therapy

EG eosinophilic gastritis, *EGE* eosinophilic gastroenteritis, *EoE* eosinophilic esophagitis, *eos/hpf* eosinophils per high-power field, *hpf* high-power field, *IL* interleukin, *RCT* randomized controlled trial, *TGF-β* transforming growth factor-β

antolimab, given monthly for eight doses (NCT03664960); a further phase 3 study in EoE is guaranteed.

5.5 Is There a Place for Anti-integrin Antibodies in EGID?

The mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) is a cell adhesion leukocyte receptor expressed exclusively by endothelial cells of mucosal venules. It helps to direct lymphocyte traffic into mucosal tissues, including the Peyer patches and the intestinal lamina propria, by binding integrin α4β7 expressed over T lymphocytes, eosinophils, and natural killer cells [99]. Vedolizumab, a monoclonal integrin α4β7 antibody approved to treat IBD, blocks mainly CD4 + T lymphocytes from binding to MAdCAM1 on intestinal endothelial cells, thus preventing both the passage and retention of leukocytes and resulting in gut-selective anti-inflammatory activity [100]. In addition, vedolizumab also blocks αE/β7 integrin [100], a marker of intraepithelial T lymphocytes and mast cells in mucosal tissues, which has been found on esophageal Th2 cells from patients with EoE [101]. Cumulative evidence suggests a potential role for vedolizumab and other anti-integrin antibodies in targeting inflammation in EGID.

The ability of vedolizumab to block eosinophil adhesion and extravasation in the gastrointestinal tract [99, 102] has been shown in some recent reports on EGID. In a first retrospective series, five adults with EGE who failed to respond to previous treatment with systemic or enteral release steroids, elimination diets, mast cell stabilizers, and immunomodulators, as well as infliximab and omalizumab in two particular patients, received vedolizumab infusions [103]. Two patients had overall clinical improvement after vedolizumab and were able to decrease or wean off systemic steroids; however, eosinophil infiltration vanished only in one patient. An additional patient had clinical improvement but refused repeated endoscopic evaluation. A second case series demonstrated that vedolizumab induced clinical and histological improvement in three out of four patients with steroid-refractory EGE [104], thus suggesting further assessment in refractory cases. Before long, an RCT should assess the effect of vedolizumab on gastric eosinophilic infiltration of patients with EGE.

As for EoE, two recent observations have reported on a 43-year-old male [105] and a 42-year-old woman who both had Crohn's disease and EoE [106]. Both patients experienced clinicohistological remission of the latter after 6–12 months of therapy.

5.6 Anti-IgE Therapy is Not Effective for EGID

The production of antigen-specific IgE promoted by a Th2-mediated class-switching of plasma cells is a central component of several allergic diseases. The monoclonal antibody omalizumab binds to free serum IgE and prevents it from binding to high-affinity receptor FcεRI over mast cell and basophil surfaces, resulting in a reduction in the amount of circulating IgE and a halt in the cascade of biochemical phenomena that trigger symptoms. Omalizumab is approved as a complimentary therapy for severe bronchial asthma and chronic urticaria. As patients with EGID usually present elevated serum levels of total and specific IgE, as well as a positive skin prick test result, targeting IgE was a logical approach deserving investigation.

Thirty adults with EoE were randomized to receive either omalizumab every 2–4 weeks (based on weight and serum level of IgE) or placebo for 16 weeks in a double-blind RCT [107]: Eosinophil counts were not altered in biopsy samples nor did they improve symptoms compared to placebo.

As for EGE, a 16-week, open-label trial of omalizumab in nine patients failed to demonstrate an immunomodulatory or inhibitory effect on allergen-specific T cells. This research did not support a major role for IgE facilitated antigen presentation augmenting allergen-specific T cell responses in EGE, even though no biopsy was performed post therapy to document changes in tissue eosinophilia [98]. More recently, the combination of omalizumab and mepolizumab was shown to control symptoms in a patient with severe asthma and EGE who was refractory to multiple therapies [109]. However, again no biopsies were taken to assess tissue changes.

6 Inhibition of JAK-Mediated Signaling as a Potential Treatment for EGID

JAKs are a family of nonspecific enzymes with tyrosine kinase activity linked to cytokine and hormone receptors. Through its ability to phosphorylate several substrates, including STAT signal transducer proteins, the JAK-STAT signaling pathway is involved in the pathogenesis of inflammatory and autoimmune diseases, including rheumatic, neoplastic, skin, and hair disorders and IBD [110]. Many cytokines involved in the pathogenesis of these disorders use JAKs to activate STAT signal transducer proteins, which penetrate the cell nucleus and bind to DNA to regulate its expression. After some preliminary results in eosinophil-related disorders, including hypereosinophilic syndrome [111], bronchial asthma [112], and eosinophilic fasciitis [113, 114], the effectiveness of the JAK inhibitor tofacitinib to induce clinical and endoscopic remission and to significantly reduce esophageal eosinophilic infiltration in a patient with all treatment-resistant EoE has been recently reported [115]. In fact, in vitro studies had already demonstrated the ability of JAK inhibitors to block the stimulatory action of IL-13, mediated by STAT6, to increase *eotaxin-3* gene

expression and its protein secretion by esophageal epithelial cells [59], similar to PPIs [116]. However, only JAK-STAT6 pathway inhibitors were able to reproduce this effect in esophageal fibroblasts, suggesting a role for JAK inhibitors in treating subepithelial fibrosis in EoE, not observed for omeprazole [59]. Further studies should evaluate the potential role of selective JAK-STAT inhibition to target both eosinophilic inflammation and fibrosis in EoE.

7 S1PR Agonists: Could Small Molecule Immunomodulatory Drugs Displace Large Monoclonal Antibodies?

After demonstrating effectiveness in several immune-mediated inflammatory disorders, some small-molecule inhibitors with the ability to specifically block intracellular signaling pathways thought to be also pivotal in the pathogenesis of EGID are sparking the interest of pharmaceutical companies. Potential advantages over monoclonal antibodies include ease of oral administration, stable structures, non-immunogenic structures, short half-lives, and lower manufacturing costs [117]. Together with JAK inhibitors, selective sphingosine-1-phosphate receptor (SP1R) modulators are promising therapies. Sphingolipids are important elements in the structure of cell membranes, and sphingosine-1-phosphate (S1P) is a sphingolipid metabolite derived from sphingosine which plays a key role in innate and adaptive immunity by regulating lymphocyte trafficking, Th17 cell polarization, dendritic cell differentiation, and migration of natural killer cells [118]. Dysregulated S1PRs are involved in the pathophysiology of immune-mediated diseases, and several SP1R modulators have been effective in multiple sclerosis, psoriasis, and IBD [119–122], among other diseases. After showing promise in the treatment of ulcerative colitis [122], etrasimod (APD334) will be the first SP1R modulator to be evaluated in EoE in a phase 2b trial (https://www.arenapharm.com/pipeline/etrasimod; consulted on April 4th, 2020).

8 PGD2 Receptor Antagonists to Treat Gut Eosinophilia

Prostaglandin D2 (PGD2) is an important chemoattractant produced and released by mast cells and exerts downstream inflammatory effects after binding to CRTH2 receptors expressed on several types of cells. Its function is to recruit and activate Th2 lymphocytes, eosinophils, and basophils towards tissues, and therefore plays an essential role in allergic diseases. Orally administered CRTH2 antagonists are being developed to treat severe asthma, and could provide a practical alternative to biological agents [123].

Timapiprant (OC000459) is a selective CRTH2 antagonist effective against eosinophilic asthma, and it has been evaluated in a double-blind, placebo-controlled RCT of 26 adults with refractory EoE [124]. After 8 weeks, significant decreases in both esophageal eosinophilia and symptoms were observed among patients treated with the active drug, as well as a trend toward normalization of endoscopic features. However, the esophageal mucosa did not return to normal. Whether longer treatment periods could provide benefit is unknown. No CRTH2 antagonist has been used in patients with non-esophageal EGID to date.

9 Potential Therapeutic Targets to be Investigated in EGID

TSLP mainly produced by the epithelium has a central role in several immune-mediated diseases, which include IBD, bronchial asthma, atopic dermatitis, and EoE [22], by promoting eosinophil activation and Th2 cytokine production. Tezepelumab is a fully human anti-TSLP antibody with favorable effects in adults with uncontrolled asthma, according to a phase 2b RCT [125]. Targeting TSLP with specific antibodies decreased eosinophilia and total immune cell infiltration in esophageal tissues of a murine model of EoE [126]. Because TSLP is also a potent chemoattractant for eosinophils, it might represent a promising pharmacological target for EGID.

Eotaxins, the most studied eosinophil chemoattractants, bind to the CCR3 receptor. An oral small-molecule selective competitive antagonist of CCR3 (GW766994) has been investigated in airway eosinophilia, with negative results [127]. As yet, no studies in EGID with these drugs have been proposed.

Finally, fibrous remodeling leads to narrow caliber esophagi and gut strictures. TGF-β plays a relevant role in this process and has been proposed as a critical target to prevent or reverse long-term consequences of fibrosis. Losartan, an antigotensin-1 receptor antagonist approved to treat high blood pressure, has demonstrated an ability to reduce the signaling of TGF-β, thus constituting a potential treatment for fibrosis in EGID [22]. An ongoing phase 2 trial with increasing doses of losartan is assessing this drug's potential to achieve endoscopic, histological, and symptomatic improvement in EoE (NCT03029091).

10 Conclusions and Future Directions

Current available therapies for EGID relieve symptoms and eosinophilic inflammation in a high proportion of patients in the short term. The release of novel formulas of topical steroids targeted at the esophageal mucosa and more efficient new step-up approaches for elimination diets will also facilitate

effective long-term maintenance of remission in a significant proportion of patients with EoE. There is much less information available for non-esophageal EGID, however.

The limitations of the current treatment options for these diseases are now being revealed: a proportion of patients do not achieve or maintain clinicohistological remission, particularly in the long term. Although dietary treatment, when effective, is the only drug-free therapy directly targeting the primary cause of EoE, patients must completely avoid some common foods widely distributed in the staple diet; a risk of developing immediate IgE-type reactions after prolonged food elimination has been described [128]. Steroid or PPI withdrawal usually induces a rapid recurrence of the inflammation, and due to concerns about long-term side effects, steroid-sparing therapies are needed.

Novel targeted therapies might potentially overcome some of the aforementioned limitations. Anti-IL-13 and anti-IL-4 biological agents are promising treatment alternatives with current phase 2 data showing an ability to treat simultaneously the multiple atopies these patients present. Despite biologicals targeting Th2 cytokines appearing to have a favorable safety profile for long-term use, monoclonal antibody-based therapy has been associated with a risk of immune-mediated effects, including hypersensitivity reactions, overstimulation, immune imbalance-derived reactions, and cross-reactivity [129], as well as loss of response due to neutralizing antibodies, which requires increased doses, shortened administration intervals, and associated immunosuppressants [130].

Small molecules preventing JAK-STAT prostaglandin receptor activation have already shown utility in other indications and may overcome some of the limitations of monoclonal antibodies. Their development in EGID is just beginning, so they represent the second generation of targeted therapies. Combinations of different treatments for patients partially responding to single approaches is still to be explored, as well as intermittent versus continuous maintenance therapy.

Apart from efficacy and safety data, the availability of novel targeted therapies in clinical practice will depend on cost, an aspect that has not yet been adequately addressed [131]. Evidence indicates it would triple that of controls for the same age group due to frequent doctor visits, diagnostic delays, requirement for endoscopy and biopsy for diagnosis and monitoring of disease activity, and medication. More expensive therapies further trigger costs for insurance companies and health systems, so cost-effectiveness studies for the different therapies are urgently needed.

Given the great expansion of targeted therapies for EGID, it will be necessary to address actively involving patients in decision-making, and following rational and realistic strategies that take into account cost-benefit balances that incorporate new effective drugs to treat these disorders. Identifying which therapeutic choices to select will become increasingly important to not only overcome the limitations of current options, but also to respond effectively to the needs of all stakeholders involved in these complex diseases.

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Compliance with Ethical Standards

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