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Immunomodulatory Therapy of Eosinophil-Associated Gastrointestinal Diseases

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Abstract

Eosinophil-associated gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EE) and eosinophilic gastroenteritis (EG), are a spectrum of increasingly recognized inflammatory diseases characterized by gastrointestinal symptoms and eosinophilic infiltration of the gastrointestinal tract. Significant morbidity is associated with the development of esophageal strictures in some patients. Immune-mediated reactions to food allergens appear to drive the inflammation in a subset of patients, especially those with solitary EE, but dietary interventions remain difficult in EE and are less effective in EG. Despite the increasing incidence of these disorders and their increased recognition by physicians, there are currently no medications that either United States or European Union regulatory agencies have specifically approved for use in EGIDs. This lack of safe and effective therapies for EGIDs is a major obstacle in the care of these patients and underscores the need for new therapeutic approaches. This review briefly discusses the currently available “off label” drug treatments for EGIDs, most notably topical and systemic corticosteroids. Pathogenesis studies of EGIDs suggest possible therapeutic targets, and conversely, clinical trials of mechanistically-targeted therapeutics give insight into disease pathogenesis. Thus, EGID pathogenesis is discussed as an introduction to mechanistically-targeted immunotherapeutics. The two biologic categories that have been used in EGIDs, anti-IgE (omalizumab) and anti-IL-5 (SCH55700/reslizumab and mepolizumab), are discussed. Since there are similarities in the pathogenesis of EGIDs with asthma and atopic dermatitis, biologic therapeutics currently in early trials for asthma management are also briefly discussed as potential therapeutic agents for EGIDs. Given the deficiencies of current therapeutics and the rapidly advancing knowledge of the pathogenesis of these disorders, EGIDs are an ideal model for translating recent advances in understanding immunopathogenesis into mechanistically-based therapeutics. Further understanding of the early events in pathogenesis is also needed to develop preventive and disease-modifying treatments.

Introduction

Eosinophil associated gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EE) and eosinophilic gastroenteritis (EG), are a spectrum of increasingly recognized inflammatory diseases characterized by gastrointestinal symptoms and eosinophilic infiltration of the gastrointestinal tract, in the absence of parasitic infection, vasculitis, neoplasm, or other known causes of eosinophilia[1]. Solitary EE is the most common EGIDs clinical entity and its incidence has dramatically risen over the past 10 years[2], in parallel to the incidence of other atopic diseases. This increase appears to be due to both greater awareness as well as actual increases in disease incidence. No specific biological factors contributing to this increase in disease incidence have yet been identified.

The symptoms of EE vary by age group. In infants and young children, abdominal pain and vomiting are predominant, whereas dysphagia is the most common complaint in preadolescents and older populations. Episodic food impaction may be the sentinel event that brings an otherwise modestly symptomatic patient to medical attention. In contrast to EE, EG is a more heterogeneous disorder in terms of anatomic location (stomach, duodenum, ileum), depth of tissue involvement (mucosal, mucularis, serosal) and predominant symptoms (abdominal pain and cramping, bloating, nausea, vomiting, early satiety, diarrhea, ascites, obstruction). Approximately 15–25% of adult EG patients have concurrent EE with symptoms of dysphagia (Lee, unpublished results).

EGIDs are strongly associated with coexisting allergic disease and between 50–75% of EGIDs patients have allergic disease or positive allergen skin tests. In particular, EGIDs is associated with both clinical and laboratory evidence of food hypersensitivity, often with positive allergen skin tests to a large number of foods. Despite this association with food allergy, few EGIDs patients have overt anaphylaxis to foods. Peripheral blood eosinophilia is also common and can be significant in a subset of patients.

The First International Gastrointestinal Eosinophilic Research Symposium published a consensus diagnostic definition of EE requiring typical EE symptoms and the finding of ≥ 15 eosinophils per high-powered field in maximally affected biopsy samples that were obtained while the patient was on maximal proton pump inhibitor therapy or with evidence of normal esophageal pH monitoring [3]. The diagnosis of EG is less well established, but we typically make the diagnosis based on patients having a subset of the above symptoms, ≥ 25 eosinophils per high powered field, and the absence of other potential causes of eosinophilia, including helminth infection. Eosinophilic infiltration of the gastrointestinal tract, as seen in EG, can also precede the onset of inflammatory bowel disease; thus, appropriate evaluation and follow-up is necessary.

Pathogenesis

Because future therapeutic approaches to EGIDs will largely be based on mechanistically-targeted therapeutics, a thorough understanding of EGIDs pathogenesis is needed. Mediators and inflammatory pathways suggested by human and animal studies point to candidate therapeutics, such as the anti-IL-5 and anti-IgE monoclonal antibody studies discussed below. Pathogenesis studies suggest possible therapeutic targets, and conversely, clinical trials of mechanistically-targeted therapeutics give insight into diseases pathogenesis.

Comprehensive reviews of EGIDs pathogenesis have been recently published[1,4]. Several features of EGIDs suggest an allergic etiology in most patients:

1. 50–75% of patients with EGIDs are atopic, with a high prevalence of food allergen-specific IgE.
2. EE disease activity is responsive to an elemental diet and resumption of an unrestricted diet results in disease recurrence.
3. The Th2 cytokines (IL-4, IL-5, IL-13), eotaxin chemokines (CCL11, CCL24 and CCL26) and inflammatory cells (eosinophils, Th2 cells, mast cells) characteristic of EGIDs are commonly found in other allergic diseases.

The most straightforward interpretation of these findings is that food allergen-driven allergic inflammation plays a major role in EGIDs pathogenesis (Figure). In this scheme, Th2-like cytokines, produced by either IgE-dependent (mast cells, basophils) or T cell-dependent pathways drive GI tissue eosinophilia. Whether one of these two pathways plays the dominant role, or if EGIDs are truly a “mixed” disorder, has not been determined[1].

Regardless of their cellular source, the Th2 cytokines expressed in EGIDs, such as IL-4, -5 and -13, drive the downstream events that result in eosinophilic inflammation. IL-4 plays a dominant role as a positive feedback for further Th2 differentiation, whereas both IL-4 and IL-13 are essential for IgE class switching and IgE expression. IL-5 is the major eosinophil active cytokine *in vivo* and positively regulates a large number of eosinophil functions, including eosinophilopoiesis, bone marrow release, activation, and survival. In contrast to IL-4, IL-13 is largely an inflammatory effector cytokine that upregulates chemokines such as CCL26 (eotaxin-3) and adhesion molecules, such as VCAM, thereby potentiating allergic inflammation.

Recent microarray analyses of eosinophilic esophagitis underscore the role of IL-13-induced CCL26 in EGIDs pathogenesis[5,6]. CCL26 was the most highly upregulated gene found in esophageal biopsies taken from EE patients, relative to healthy control subjects. Real time PCR, *in situ* hybridization and ELISA confirmed this increased expression of CCL26 in EE tissue. Furthermore, CCL26 levels correlated with esophageal eosinophil number. In all, in EE 344 genes were up-regulated and 230 genes were down-regulated, relative to normal esophageal tissue, and this transcriptome signature was reproducible among EE patients. Although upregulation of IL-13 was not found in the initial microarray analysis, subsequent real time PCR studies found that IL-13 is upregulated in EE[6]. Furthermore, treatment of primary esophageal epithelial cells with IL-13 induced a similar transcript signature to that found in EE patients, with notable upregulation of CCL26 expression. Lastly, successful treatment of EE with swallowed fluticasone was associated with normalization of the EE transcript signature. These results suggest that IL-13, CCL26, or the CCL26 receptor, CCR3, are potential targets for developing therapeutics.

Under the EGIDs umbrella, multiple specific clinical subsets exist (e.g. EE vs. EG, allergic vs. non-allergic), with each subgroup likely having somewhat different details in their pathogenesis. Despite these differences, the microarray transcript profiles from both allergic and non-allergic EE subjects are similar, suggesting that there is a final common pathway leading to eosinophilic tissue inflammation. As additional clinical trials in EE are performed, the identification of “responder” subsets to a specific mechanistically-targeted therapeutic may yield insights into which inflammatory pathways are dominant in a given clinical subset.

Established Therapies for EGIDs

Food allergy appears to play a central role in driving the allergic inflammation in a subset of EGIDs, especially in pediatric patients with EE, as evidenced by symptomatic and histologic improvement with initiation of elemental diets[7]. Immunologic reactions to food allergens in these disorders are both IgE- and cell-mediated. Current approaches to dietary restriction include, restrictions based on *in vivo* and/or *in vitro* testing for food-specific IgE, patch testing for cell-mediated reactions to food allergens[8], restriction of the 6 most common food allergens[9], or initiation of elemental diets. Although food allergen avoidance can be helpful in the management of a subset of patients with EGIDS, namely children with EE, identification of triggering food allergens and maintenance of dietary restrictions remain prohibitive in many cases[10]. In addition, dietary restrictions in adults with EE appear less effective[11], although data is limited. Disease-modifying approaches to treatment of food allergy, including recent work with sublingual and oral immunotherapy to food allergens in IgE-mediated food reactions, may be beneficial, although current trials are focused on predominantly IgE-mediated diseases[12].

Aeroallergen sensitization may also play a role in EGIDs, specifically EE, based on animal models[13] and one anecdotal report of a patient with seasonal exacerbations of EE coincident with sensitization and exposure to seasonal aeroallergens[14]. While allergen immunotherapy

is beneficial for the treatment of IgE-mediated reactions to aeroallergens, there is no data supporting a role for the management of EGIDs.

Despite the increasing incidence of EGIDs and its increased recognition by physicians, there are currently no medications that either United States or European Union regulatory agencies have specifically approved for use in EGIDs. EGIDs specialists have generally used available medications, such as inhaled corticosteroids delivered to the esophagus by swallowing, in an “off label” manner. Despite the increased recognition of EGIDs as an important clinical entity, as of this time, only one blinded controlled therapeutic EGIDs clinical trial has been published [15]. The lack of safe and effective therapies for EGIDs is a major obstacle in the care of these patients and underscores the need for new therapeutic approaches.

EGIDs are highly responsive to moderate dose systemic corticosteroids (e.g. 0.5–1 mg/kg prednisone), particularly in newly diagnosed patients who are corticosteroid naïve. Unresponsiveness to systemic corticosteroids at the time of initial diagnosis should be cause to reexamine the diagnosis. Because long-term use of systemic corticosteroids results in multiple sequelae, EGIDs specialists have utilized inhaled topical corticosteroid preparations “off label” in an analogous manner to their use in asthma. Both swallowed fluticasone[15] as well as viscous budesonide[16] are effective in EE and have been shown to reduce both tissue eosinophilia as well as EE symptoms. Swallowed fluticasone causes a clinical and histologic remission in approximately 50% of patients; however, a sizable group of non-responders were found, which were particularly notable in the atopic EE subgroup[15]. Because of the difficulty in using a metered dose inhaled to deliver swallowed fluticasone, it is unclear how much of this non-responder effect is a function of medication compliance or dose effect, rather than a true non-responder disease subset. The major complication of treatment with topical fluticasone is esophageal candidiasis in a small number of treated patients, although this tends to be asymptomatic and is easily treated with anti-fungal medications[15,17]. Analogous to this use in EE, there are case reports examining the use of budesonide to treat EG[18,19], including forms targeting activity to the ileum and colon. Among 20 children treated with swallowed viscous budesonide (1–2 mg/day) for EE over 3–4 months, one child with associated mild hypogammaglobulinemia developed esophageal candidiasis, but there were no other adverse events reported[16]. The larger doses of budesonide required to treat EG (typically 6–9 mg/day), coupled with its relatively high systemic bioavailability, however, may result in relatively frequent toxicity when used for several years (Prussin, personal observation).

Conventional immunomodulators

Because conventional small molecule immunomodulators are more available and have lower cost than biologics, they should be considered as potential candidates for future EGIDs clinical trials. This is particularly true for EG, where there are fewer treatment options available. Unfortunately, at present there are no published controlled studies of any conventional immunomodulator in EGIDs. Azathioprine and 6-mercaptopurine are well accepted for use in inflammatory bowel disease, but their use in EG is limited to case reports or small case series [20,21]. Thus any formal evidence based assessment of their activity in EGIDs is not possible.

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are clinically effective in atopic dermatitis and has been shown to lower tissue eosinophil counts in this disorder. In vitro studies demonstrate that calcineurin inhibitors decrease both Th2 and mast cell cytokine expression, suggesting that they may have clinical activity in EGIDs[22,23]. However, several reports have associated tacrolimus use with the development of secondary EGIDs and food hypersensitivity when the drug is used in the setting of liver transplantation[24,25]. Patients with this secondary EGID syndrome typically have coexisting peripheral eosinophilia and their disease remits upon reduction or discontinuation of the drug. It is not clear if this association

is limited to tacrolimus or to the clinical setting of liver transplantation. Further clinical studies are needed to determine if these drugs can be safely used in EG.

Investigational Biologic Therapeutics

Although the increased incidence of EGIDs has made it a viable clinical target for drug discovery, at present most of the candidate therapeutics were initially developed as potential asthma therapeutics. Given the similarities between EGID and asthma pathogenesis, it is a reasonable strategy for investigators to identify potential EGID therapeutics from the investigational asthma drug pipeline. The combined impetus of greater EE incidence and improved understanding of EGID pathophysiology should foster the development to additional drugs specifically targeted at EGIDs. To date, only 3 biologic agents have been reported in open-label clinical trials for the treatment of EGIDs: humanized monoclonal antibodies against IL-5 (mepolizumab and SCH55700) and IgE (omalizumab). Since these initial studies were performed, SCH55700 has been given the generic drug name reslizumab.

Anti-IL-5

Based on the function of IL-5 in the development, differentiation, mobilization, activation, and survival of eosinophils[26] and pre-clinical studies in mice[13,27], therapeutics targeting IL-5 are obvious candidates for trials in patients with EGIDs[28]. Initial trials using anti-IL5 monoclonal antibodies (SCH55700 or mepolizumab) to neutralize IL-5 in the treatment of asthma resulted in diminished numbers of eosinophils in the peripheral circulation, but failed to significantly diminish tissue eosinophils or improve asthma control[29–31]. Trials of mepolizumab in the treatment of atopic dermatitis also failed to improve symptoms[32,33]. In contrast, a recent randomized, double-blinded, placebo-controlled trial of the humanized anti-IL-5 monoclonal antibody, mepolizumab, for hypereosinophilic syndrome demonstrated efficacy as measured by lower systemic steroid requirement to maintain disease control[34].

A pilot study treating 4 patients with eosinophilic gastroenteritis with a single dose of humanized anti-IL-5 monoclonal antibody (SCH55700) resulted in a decrease in peripheral eosinophilia (mean decrease of 70%) and tissue eosinophilia (50–70% decrease in 3 of 4 subjects), but minimal improvement in symptoms[35]. Interestingly, one patient had a 43% increase in gastrointestinal eosinophil counts 4 weeks after treatment. In addition, 7–8 weeks after treatment, 2 of 4 subjects had a significant increase in peripheral eosinophil counts and worsening of their baseline symptoms[36].

The first reported patient with eosinophilic esophagitis treated with the humanized anti-IL-5 antibody, mepolizumab, was an 18 year male with a lifelong history of dysphagia, persistent vomiting, and a severe stricture on endoscopy, who failed to respond to dietary restrictions or topical or systemic corticosteroids[37]. As part of an open-label trial, he received 3 doses of mepolizumab at 4-week intervals. On this regimen, there was a >10-fold decrease in the mean number of tissue eosinophils, diminished gross inflammation and stricture on endoscopy, improvement in symptoms with cessation of vomiting, and advancement of his diet to solids.

A follow-up, open-label, phase I/II trial in 4 adults (including the 18 year old male in the original report) with eosinophilic esophagitis similarly demonstrated promising results[38]. These patients had at least 9 years of symptoms, were refractory to standard therapies (except 1 who had no previous treatment), and had evidence of food-specific IgE, but no history of food-induced anaphylaxis. Treatment with 3 doses of mepolizumab (750 mg intravenously), at 4 week intervals, resulted in a decrease in peripheral eosinophils (6-fold), esophageal eosinophils (6-fold reduction in maximal number), and symptomatic improvement. Of note, however, is that the maximal number of eosinophils in esophageal biopsies decreased, but to a level (20–38/hpf) that is still considered diagnostic for EE. While the major goal of symptomatic

improvement was reached, it is unclear whether such levels may still carry a risk of continued fibrosis and disease progression. Neither plasma IL-5 levels nor plasma CCL26 levels predicted response to mepolizumab. Unlike the previous study with the anti-IL-5 antibody, SCH55700, [36] rebound eosinophilia was not demonstrated 12 weeks after the last treatment with mepolizumab.

One randomized, placebo-controlled, double-blind study of mepolizumab in the treatment of adults with EE has been reported[39]. Six patients were randomized to receive placebo and 5 were randomized to receive mepolizumab. Mepolizumab was administered at 0 and 7 days (750 mg/dose), and if tissue eosinophil counts remained >5/hpf, two additional doses (1500 mg/dose) at 4 week intervals were administered. On this regimen, mepolizumab resulted in a 67% reduction in tissue eosinophils (mean 82 eosinophils/hpf to 27 eosinophils/hpf), compared to a 25% reduction in the subjects treated with placebo (mean 61 eosinophils/hpf to 45 eosinophils/hpf). Peripheral blood eosinophils counts also decreased in subjects treated with mepolizumab, but not with placebo. A subset of patients receiving mepolizumab reported improvement of swallowing difficulties, 2 of 5 patients, compared to 1 of 6 patients receiving placebo. The level of reduction of esophageal eosinophils reported is similar to that reported in the airways of asthmatics treated with mepolizumab, who failed to demonstrate improved disease control with treatment.

Larger randomized, controlled trials are needed to further clarify the efficacy and safety of this therapy and to clarify its role in the long-term management of patients with EGIDs, including use in patients at earlier stages of disease and with less severe presentations. The finding of elevated IL-5 levels after treatment with mepolizumab in a recent report[40], and the previous report of rebound eosinophilia after cessation of therapy, also raises questions about long-term dosing strategies if long-term therapy is required. If future therapeutic regimens use anti-IL-5 therapy, unless specific “responders” to anti-IL-5 can be identified, targeting of additional mediators would likely be needed as well.

Anti-IgE

Patients with EGIDs frequently have multiple food-specific IgE levels detectable by skin testing and/or *in vitro* testing and, particularly with EE, respond to dietary restrictions. In addition, mast cell numbers are increased in esophageal biopsies from patients with EGIDs [41], activated mast cells are identified by electron microscopy of esophageal biopsies of patients with EE[42], and an association between mast cell numbers and degree of esophageal eosinophilia and epithelial hyperplasia has been described[5]. A role for IgE in pathogenesis has been hypothesized, although EGIDs clearly are not exclusive or typical type I hypersensitivity disorders.

Omalizumab is a humanized therapeutic monoclonal antibody that binds to IgE, thus preventing IgE from activating mast cells and basophils and decreasing the concentration of high affinity IgE receptors on these cells. Omalizumab is used in severe atopic asthma that is not controlled by maximal medical therapy using conventional asthma drugs. At present, omalizumab is the only clinically available anti-IgE therapeutic.

Anti-IgE lowers eosinophil counts in both the blood and lungs of asthmatic subjects[43], which suggested that anti-IgE could be a potential therapeutic approach in EGIDs. To address this question, we recently examined the potential efficacy of omalizumab in a 16 week open label study of 9 subjects with allergic eosinophilic gastroenteritis[44]. Omalizumab was associated with a 35–45% drop in peripheral blood eosinophil count as well as larger magnitude 60–70% decreases in duodenal and antral eosinophils. In contrast, esophageal eosinophils were modestly increased during the study, providing further support that EE and EG are distinct clinical entities with different pathophysiologic features. Although the study was not designed

to meaningfully measure symptom improvement, EGID symptom scores were significantly decreased. Importantly, it also supports a role for IgE in the pathogenesis of EGIDs.

To examine the role of food allergen activation of IgE-dependent pathways, *in vitro* studies of basophil activation were performed. Omalizumab increased the concentration of food allergen required to activate basophils by >150-fold. Similarly, basophil bound IgE decreased by 98% during the study. The high serum IgE of many of the subjects (400–700 kIU/L) may have reduced the drug's effectiveness. Omalizumab is dosed in proportion to a patient's serum IgE, and its efficacy is directly related to its ability to lower free IgE[45]. Therefore, omalizumab is unlikely to be effective in EGID patients with a serum IgE above 700 kIU/L. In our study, free IgE was only decreased by 75–80%, which is lower than that noted in the pivotal asthma trials. Thus, second generation anti-IgE therapeutics with greater capacity to block IgE may have greater efficacy in EGIDs.

Anti-TNF

Anti-TNF therapies are currently approved for the treatment of inflammatory bowel disease, rheumatoid and psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Trials of anti-TNF therapy (etanercept) in patients with refractory asthma and elevated TNF expression in monocytes, a small subset of asthmatics, have also been promising, although of benefit only to a small subset of patients[46]. Since esophageal epithelial cells in patients with active EE express significantly higher levels of TNF relative to controls[41], a recent report describes the results of treatment of 3 adults with severe, corticosteroid-dependent EE[39]. The 3 patients were taken off all treatments for EE during a 4 week run-in period, then treated with 2 doses of infliximab (5 mg/kg) spaced 2 weeks apart as monotherapy. With this treatment, 2 patients had very mild improvement in symptoms, while 1 had worsening symptoms. There was no significant decrease in eosinophils or mast cells in the 2 responders and there was a modest decrease in TNF expression in esophageal epithelial cells. As a result, this approach does not appear promising for monotherapy of EE, however, use at higher doses and/or for longer periods of time may be necessary to demonstrate efficacy. Alternative agents for TNF blockade may also be beneficial. Similar to asthma, it may be that only a subset of patients with EE will respond to disruption of TNF. Identification of predictors of response and combination with other agents may be of greater benefit.

Candidate Biologic Therapeutics

There are several biologic agents currently in phase I or II trials for asthma that have the potential to play a role in the treatment of EGIDs as well and are candidates for clinical trials in the treatment of EGIDs.

Anti-IL-5 Receptor

Anti-IL-5 receptor α antibodies are currently in phase I trials for asthma and are reported to deplete eosinophils through ADCC, rather than neutralizing IL-5 activity, as does mepolizumab. In a preliminary study, low doses of an anti-IL-5 receptor monoclonal antibody, MEDI-563, resulted in a decrease in peripheral blood eosinophils that persisted for at least 56 days[47]. In addition, the antibody was found to bind to >90% of lung eosinophils in mild asthmatics[48]. Although no trials in EGIDs have been reported, this approach likewise could prove to be beneficial for EGIDs.

IL-4/IL-13 Antagonists

Disappointing responses of asthmatics in clinical trials with antagonists of Th2 cytokines (IL-5 and IL-4) has led to the suggestion that inhibiting multiple cytokines may be needed for adequate responses. The utilization of the IL-4 Receptor α chain for signaling through the IL-4

and IL-13 receptors has been used in designing novel therapeutics for asthma. A recombinant IL-4 variant ligand, pitrakinra, has been developed to competitively inhibit activation of both IL-4 receptor and IL-13 receptor signaling. Phase II trials using both subcutaneous injection and inhalation of pitrakinra have demonstrated diminished drops in FEV1 following an allergen challenge when compared to placebo groups[49]. Further trials are ongoing for asthma and atopic dermatitis. EGIDs would be another target disease for future trials of pitrakinra or similar biologic agents.

Other potential targets for treatment of EGIDs, based on the current understanding of the pathophysiology of the disorder, include:

CCR3 (eotaxin receptor) antagonists, eotaxin (CCL26, CCL11, CCL24) antagonists, and $\alpha 4\beta 7$ antagonists, all involved in recruitment and homing of eosinophils to the gastrointestinal tract; IL-13 antagonists, to block the upstream mediator, IL-13, that leads to eotaxin expression and reproduces the EE transcriptome when used to treat epithelial cells.

Anti-CD25 monoclonal antibodies and interferon- α are additional agents that are available, but warrant further investigation in the treatment of EGIDs

Future Therapeutic Trials

The outcome measures of therapeutic trials of biologics for the treatment of EGIDs need to be selected carefully. Most studies to date monitor peripheral blood and target organ eosinophil counts, symptom improvement, and quality of life measures. There are currently no biomarkers identified that are predictive of long-term progression of esophageal fibrosis and stricture formation. Although symptom control is clearly the initial objective in any therapeutic trial for EGIDs, prevention of long-term sequelae from progression is also critical. Improvements in our understanding of pathogenesis and identification of biomarkers predictive of disease control and progression should improve future trials. Therapeutic trials of agents that target single molecules may prove insufficient to optimally control symptoms and disease progression. Future trials may need to evaluate the use of multi-target therapies, either using two agents or with the development of single agents that target more than one molecule (e.g. pitrakinra).

Finally, it is important to note that all treatments identified to date and in clinical trials are intended to control disease. The early events in the pathogenesis of EGIDs are still poorly understood. There is preclinical data in animal models that suggest that epicutaneous[50] or respiratory sensitization[13] to allergens can lead to development of EGIDs. However, the basis of a genetic predisposition to develop these disorders and the environmental exposures that trigger development of disease are unknown. Further studies to clarify the early events triggering EGIDs development and genetic predisposition, and the development of disease-modifying therapies should be a major focus of future studies.

Conclusions

EGIDs, and in particular EE, are an increasingly recognized group of clinical disorders for which current therapeutic approaches are inadequate. Swallowed fluticasone, which is currently the best characterized treatment, is only effective in about half of patients with EE. Future EGIDs drug discovery will largely be focused on mechanistically-targeted drugs. As such, current studies of EGIDs pathogenesis are of critical importance in defining future therapeutic targets. The large pipeline of mechanistically targeted asthma and allergy drugs should be a plentiful source of potential future therapeutics. Given the increased incidence of EE, EGIDs should be recognized as a distinct clinical entity worthy of a dedicated program of drug discovery.

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Therapeutic Targets in EGIDs

Figure 1.