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The role of biologics in pediatric food allergy and eosinophilic gastrointestinal disorders

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Abstract

Continuing insight into the molecular mechanisms of atopic disorders has enabled the development of biologics to precisely target these diseases. Food allergy (FA) and eosinophilic gastrointestinal disorders (EGIDs) are driven by similar inflammatory molecular mechanisms and exist along the same atopic disease spectrum. Therefore, many of the same biologics are being investigated to target key drivers of mechanisms shared across the disease states. The enormous potential of biologics for the treatment of FA and EGIDs is highlighted by significant increases in the number of ongoing clinical trials, over 30, evaluating their use in these disease states as well as the recent FDA approval of dupilumab for the treatment of eosinophilic esophagitis (EoE). Here we discuss past and current research into the use of biologics in FA and EGIDs and their potential role in improving treatment options in the future with the need to have biologics widely clinically available.

Keywords

Food allergy; eosinophilic gastrointestinal disorders; biologics; oral immunotherapy; eosinophilic esophagitis; eosinophilic gastritis; eosinophilic enteritis; eosinophilic colitis

Introduction

The prevalence of T helper 2 (T_H2) cell-driven atopic conditions such as food allergy (FA)[1] and eosinophilic gastrointestinal disorders (EGIDs)[2] has increased over the last several decades. FA alone affects approximately 33 million people in just the US[1], with approximately 1 in 20 of those with FA experiencing concomitant eosinophilic esophagitis (EoE), a 125-fold increase in prevalence over the general population[3]. This increased prevalence is likely due to substantial mechanistic overlap between not only the two conditions, but also other elements of the atopic march, which also include asthma and atopic dermatitis (AD). Indeed, many biologics that are under investigation in FA and EoE were first studied in asthma or AD, with their utility in the treatment of other atopic diseases being evaluated as early as 2003 (Figure 1).

With a better understanding of the mechanisms that drive atopic diseases, there has been an increased interest in using biologics that target the shared T_H2, and to a lesser extent, non- T_H2 molecular pathways (Figure 2). Atopic diseases can often co-exist; the earliest manifestation is AD which can arise in infancy. Skin barrier defects that are closely linked to the development of AD are also associated with the development of FA and EoE[4, 5]. These skin barrier defects induce the secretion of ‘alarmins’, signaling molecules such as IL-25, IL-33, and TSLP (Figure 2), which lead to downstream activation of type 2 allergic inflammation and pathological symptoms in atopic diseases, including AD and EoE (Figure 3). This is promising for the treatment of atopic diseases that share similar molecular mechanisms as agents selectively inhibiting such pathways could be used to simultaneously treat multiple related disease states. For example, the recent FDA approval of dupilumab for EoE in May 2022, a drug already approved for treatment of moderate-to-severe AD, nasal polyposis, and asthma. Similarly, Omalizumab has been approved for allergic asthma, chronic spontaneous urticaria, and is being investigated in FA. These

examples have encouraged the investigation of biologics in other atopic diseases such as FA and non-esophageal EGIDs. Here, we discuss the role of biologics in FA and EGID in advancing treatment while highlighting key knowledge gaps that remain.

Role of Biologics in Food Allergy

Current knowledge of the mechanisms of FA stems primarily from animal models, however, studies monitoring the response to immunotherapy and biologics and studies on natural resolution in humans[6] have helped clarify how tolerance is regulated. Respiratory, skin, and gut barrier disruption and dysfunction are key factors which allow food allergens to permeate through, promote the shift from tolerance to sensitization, and eventually activate antigen-specific B cells and downstream effector responses from eosinophils, basophils, and mast cells[7] (Figure 3). Cytokines and alarmins produced by dysregulated epithelial cells and activated antigen presenting cells during sensitization, including IL-25, IL-33, and TSLP, induce naïve CD4+ T cell differentiation into T_H2 cells and drive production of additional proinflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13. Large amounts of these T_H2 cytokines produced, in part, by innate lymphoid cells [8], disable the induction of tolerance by T cells and drive the recruitment and proliferation of effector cells[7]. The key drivers of the clinical symptoms associated with an allergic reaction include histamine, leukotrienes, cytokines, and prostaglandins. These inflammatory mediators are released upon degranulation of activated basophils and mast cells after exposure to an antigen (food allergen) resulting from crosslinking of antigen-specific IgE complexes on the cell surface[9].

Although numerous studies have demonstrated the safety and efficacy of oral immunotherapy (OIT) for the treatment of FA[10–15], adverse events (AEs) to OIT are common, especially during the initial build up phase[16–18]. This combined with the burden and stress of daily consumption of the allergenic food can make long-term adherence difficult[17, 18]. Furthermore, some patients may not tolerate OIT or have difficulty achieving desensitization goals, potentially due to differences in disease endotypes[19, 20]. Biologics have the potential to be used in a non-allergen-specific manner by targeting the underlying mechanisms driving the allergic state thus carrying the advantage of dampening allergic inflammation triggered by many allergens (food and environmental) when used alone or in combination with OIT (Table 1). To date, the most widely investigated strategy to minimize AEs associated with OIT has been the use of anti-IgE biologics[21–26].

Anti-IgE Therapy

Talizumab

The first trial of biologics in FA evaluated the use of talizumab (TNX 901), an anti-IgE biologic, in 12–60-year-old patients with a history of peanut allergy (n=84). Treatment with talizumab was well-tolerated and significantly increased the reaction-eliciting dose of peanut protein from baseline to week 14 to 16 in those receiving 12 weeks of talizumab 450 mg therapy compared to placebo (mean increase, 710 mg vs 2627 mg; $p<0.001$), with increasing doses of talizumab associated with greater increases in tolerated dose ($p<0.001$)[27]. Although these findings supported the efficacy of talizumab, research has since shifted toward newer generations of anti-IgE biologics.

Omalizumab and Ligelizumab

Following in the footsteps of talizumab, the anti-IgE antibody omalizumab has emerged as the most widely investigated biologic in the setting of FA. Omalizumab is currently approved for the treatment of several atopic conditions, including moderate-to-severe persistent asthma in patients aged 6 years and older, chronic spontaneous urticaria in those aged 12 years or older, and nasal polyps in adult patients aged 18 years and older. The most common approach that has been studied for its incorporation in the treatment of FA is a short course of the agent prior to the initiation of OIT. In addition to improving the safety of OIT to single foods such as peanut and milk, pre- and concurrent treatment with omalizumab has shown promise in significantly reducing the time required to reach target maintenance doses of OIT[23, 28].

Treatment with omalizumab prior to multi-allergen OIT to 2 or more foods has also been investigated in several trials[29–33]. Similar to findings of single-allergen therapy, a phase 1 study of 4–15-year-old multi food allergic children, pre-treatment with omalizumab facilitated a faster time to maintenance dose compared to multi-allergen OIT alone (median time 67 weeks vs 85 weeks, respectively)[29, 11]. Furthermore, in the phase 2 MAP-X clinical trial, in 4–15-year-old children allergic to 2–5 foods, adjunct omalizumab improved the safety of multi-allergen OIT, reduced the severity of AEs, and lowered median per-participant percentage of their OIT doses associated with any AE (27% vs 68% without omalizumab; p=0.0082)[30]. Gastrointestinal side effects, the most common type of AE during OIT, were diminished with the use of omalizumab (22% vs 54% without omalizumab; p=0.008), though not prevented. Omalizumab also increased the ability to pass a DBPCFC to at least 2 g food protein for 2 or more foods after 36 weeks (83% vs 33% without omalizumab, OR: 10, CI: 1.8–58.3, p=0.004). In line with the improved speed and safety of OIT escalation via adjunct omalizumab for multi-allergen OIT, long-term follow-up studies also demonstrate that omalizumab-facilitated multi-allergen OIT improves patient quality of life[32, 33]. Reported cases of EoE in some studies is a notable concern with OIT[34]; however, long-term follow-up is critical to capture the true incidence of EoE, which can occur after completion of study, during long-term maintenance.

Omalizumab has also been studied in a non-antigen-specific manner. In an observational efficacy study, 15 patients with severe allergic asthma and concomitant FA treated with omalizumab as monotherapy had an 8.6-fold increase in the reaction threshold dose across 16 foods, as well as a reduction in reactions related to accidental ingestions (47 in the 4 months before treatment down to 2; p <0.001)[35]. In an Italian cohort of 54 children with severe allergic asthma and FA, omalizumab monotherapy for approximately 5 months allowed 44% of participants to improve threshold sensitivity to culprit foods[36]. OUtMATCH (NCT03881696) is a prospective, phase 3 study investigating the safety and efficacy of omalizumab in multi-FAic children and adults (1–55 yo) in 3 stages. Stage 1 will assess monotherapy of omalizumab for 16 weeks compared to placebo[37]. Stage 2 will assess omalizumab facilitated multi-allergen OIT compared to omalizumab monotherapy. Stage 3 will assess the ability to switch to real-life food equivalents. The trial is currently ongoing and will provide much needed data on monotherapy and combination approaches, as well as long term outcomes.

Approval of self-administration of omalizumab at home for asthma, chronic idiopathic urticaria, and nasal polyposis, has improved access to omalizumab, and has proven to be cost effective[38]. These factors also make omalizumab an attractive treatment option for FA patients.

Despite the significant benefits to speed and safety of adjunct omalizumab, data on efficacy in promoting sustained unresponsiveness (SU) has been less promising. Similar to findings with OIT alone, sustained desensitization in omalizumab-facilitated multi-allergen OIT in the M-TAX study is more likely to occur with sustained multi-allergen OIT dosing in comparison to discontinuation of OIT dosing (85% with continuation of OIT dosing vs 55% with discontinuation, (OR: 4.5, CI: 1.1–19.3, p= 0.03) in 4–55-year-old patients[31]. Ligelizumab, another anti-IgE agent with higher binding affinities for free IgE compared to omalizumab, is currently under investigation as monotherapy in a phase 3, 52-week study for peanut allergic patients 6–55 years of age (NCT04984876)[39] and may hold promise for food allergy children and adults.

Anti IL-4 and IL-13

Dupilumab

Dupilumab is an anti-IL-4 receptor alpha (IL-4Rα) antibody that is FDA approved for moderate to severe asthma in patients 6 years or older, moderate to severe AD in patients 6 months or older, EoE in patients 12 years or older, and chronic rhinosinusitis with nasal polyps in adults. IL-4Rα is the receptor for the pro-atopy cytokines IL-4 and IL-13, thus making it an ideal target in various allergic diseases including FA. Dupilumab has potential benefits over anti-IgE therapy through a wider inhibitory impact on the allergic inflammation pathway.

There are several clinical trials recently underway assessing its efficacy with or without concomitant peanut and milk OIT as well as in multi-allergen OIT. A clinical trial using dupilumab as monotherapy for peanut allergic patients aged 6–17 years old was recently completed (NCT03793608) with results currently pending. Dupilumab's potential as an adjunct treatment with OIT is currently being examined in 2 phase 2 clinical trials, a study in peanut allergic children aged 6–17 (NCT03682770) and the MAGIC study in milk-allergic individuals aged 4–50 years old (NCT04148352). In a novel phase 2 trial, the COMBINE study (NCT03679676), children and adults aged 4–55 years old are randomized to the sequential use of omalizumab and/or dupilumab to target both the IgE and IL-4/13 pathways during multi-allergen OIT to understand safety and efficacy of combination therapy. Given dupilumab's recent approval for use in EoE, it is of great interest to see whether GI side effects are mitigated during OIT.

Optimal dosing for biologics

While the use of omalizumab in FA has largely followed the dosing guidelines used in allergic asthma based on patient weight and total IgE[23, 28, 30], the optimal dosing is still under investigation. Previously a retrospective analysis of 181 patients undergoing omalizumab as adjunct therapy with OIT found that the ideal dose of omalizumab was best

predicted by weight-based dosing, without adjusting for IgE[40]. Ongoing studies such as the BOOM trial (NCT04045301) aim to understand if weight-based dosing is more effective in FA compared to weight and IgE-based dosing[40]. Alternatively, fixed dosing of omalizumab was investigated in the MIMIX phase 2 clinical trial. Participants with multi-FAs were given a fixed dose of omalizumab (150 mg, 3 doses, every 4 weeks; similar to chronic idiopathic urticaria dosing) and a multi-allergen OIT with maintenance dose of either 300 or 1200 mg. In the ITT population, 70% of participants showed increase by 25% in sIgG4/sIgE ratios after just 18 weeks of therapy. Further analysis showed that standard omalizumab (asthma-based dosing) facilitated success at higher maintenance doses, but did not have a significant impact at lower OIT doses[41]. Although these studies have largely focused on omalizumab, similar issues exist for other biologics, highlighting the need for further studies on the optimal dosing of biologics for individual diseases.

Eosinophilic Gastrointestinal Disorders during Food Allergy Therapy

Asymptomatic gastrointestinal eosinophilia often coexists with FA, with published rates of 24–43%[42, 43] and is comparable histologically to EoE[44]. FA may develop in individuals with EoE during periods of food elimination[45] and, conversely, EoE and asymptomatic gastrointestinal eosinophilia may develop following successful oral challenge, introduction of a previously avoided IgE-mediated food allergen, and OIT[46, 47]. A pilot study investigating 20 adults undergoing peanut OIT in the POISED cohort found OIT-induced gastrointestinal eosinophilia is usually transient and asymptomatic with one adult developing EoE[48]. Most cases of treatment-associated disease fortunately resolve with dose modification or cessation of OIT[49], though a small subset may have EGIDs that persist after stopping OIT, suggesting there may be a non-OIT food trigger[50]. The impact of biologics on OIT-induced gastrointestinal eosinophilia is of particular interest and currently under investigation using the minimally invasive esophageal string test (NCT04943744, NCT04148352).

Role Of Biologics In Eosinophilic Gastrointestinal Disorders

In healthy individuals, eosinophils are found throughout the gastrointestinal (GI) tract with the notable exception of the esophagus[51]. Eosinophil counts do not normally rise above 5 eosinophils per high-power field (eos/hpf) in the esophagus, 30 eos/hpf in the stomach[52], and 26 eos/hpf in the duodenum[42]. Elevation of eosinophils in the GI tract with the presence of clinical symptoms suggests the presence of EGIDs[53] including EoE, eosinophilic gastritis (EoG), and eosinophilic enteritis (EoN) which affect 52[54], 5.1[55], and 28[54] people per 100,000, respectively.

EoE is defined clinically and pathologically as the presence of gastrointestinal symptoms (nausea, vomiting, food impaction, dysphagia) with 15 or greater mucosal eosinophils per high power field in biopsies taken at any level of the esophagus, in patients with no other identified cause of esophageal eosinophilia such as gastroesophageal reflux disease, parasitic and fungal infections, Crohn’s disease, celiac disease, and connective tissue disease, among others. Although not required for diagnosis, additional histologic features include eosinophil density, basal zone hyperplasia, eosinophilic abscesses, eosinophil surface

layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. These features comprise the EoE histologic scoring system (EoEHSS)[56] that is both reliable[57, 58] and treatment-responsive[59–64]. In addition to proton pump inhibitors (PPIs), dietary elimination of 'identified' offending foods, endoscopic dilation, and topical corticosteroids (TCS) have been a mainstay of treatment for EoE[65]. However, TCS induces Candida in esophagitis in 5–30% of patients[66], can induce adrenal insufficiency after prolonged use in 5–43% of patients[67, 68] and can lose efficacy with long-term use[69], resulting in problems with adherence, cost, and recurrence of disease which may lead to consideration of biologics[68, 70–75].

Several biologics are used or being investigated in clinical trials for the treatment of EoE which act on the cytokines and cell receptors that govern the production and homing of eosinophils (Table 2). IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are cytokines that are vital in eosinophil development[76, 77]. IL-5 is the most specific cytokine for eosinophils and acts at multiple functional levels to impact eosinophil production, activation, and survival[78]. Other cell surface structures are relatively specific for eosinophils, such as CC-chemokine receptor 3 (CCR3), which mediates eosinophil chemotaxis in response to eotaxins, and sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8), whose engagement induces the apoptosis of activated eosinophils[79, 80]. Epidermal growth factor (EGF) module containing mucin-like hormone-like receptor 1 (EMR1) is a surface receptor that is unique to the eosinophil and represents a potential therapeutic target in eosinophilic diseases[81]. Furthermore, epithelial cell-derived alarmins IL-25 (also known as IL-17E), IL-33, and thymic stromal lymphopoietin (TSLP) promote eosinophilopoiesis by increasing IL-5 production by group 2 innate lymphoid cells (ILC2)[82]. Extravasation of eosinophils out of the circulation and into tissue sites is dependent on the function of integrins and their counter-ligands on activated endothelium and eosinophil-selective chemoattractants such as the eotaxins[83]. Notably, eotaxin-3 is markedly induced by IL-13, providing a synergistic mechanism by which T_H2 and ILC2 cells, co-producing IL-5 and IL-13, regulate tissue eosinophilia[84].

In contrast to EoE, our understanding of the pathophysiology of non-EoE EGIDs is hampered by several important factors, including small sample size due to low disease prevalence, non-specific symptoms (such as early satiety, abdominal pain, nausea, vomiting, and diarrhea)[85] that may lead to diagnostic delay, and a lack of validated patient-reported outcome measures. A poor response to elimination diets and topical steroid preparations often necessitates systemic steroid use, underlining the need for effective new treatments for these diseases. In fact, many of the biologics studied in EoE have also been trialed in EoG and/or EoN[52, 86–90].

Anti-IL-4 & 13

Dupilumab

Antibodies targeting IL-13 in adults were shown to significantly reduce eosinophilic inflammation[60, 91], with a reduction in histologic and endoscopic features after treatment compared to placebo[60]. Dupilumab with dual IL-4 and IL-13 blockade led to promising results in a phase 2 study of 47 adult subjects with EoE and 12 weeks of treatment

with dupilumab reduced peak esophageal intraepithelial eosinophil counts by 107.1% (CI: 73.0–141.2 p= <.0001), EoEHSS grade 68.3% (CI: 50.3–86.2 p= <.0001), and endoscopic reference scores by 1.6 points (CI: −2.5 to −0.7; p= .0006)[61]. A phase 3 study has confirmed histologic improvements with dupilumab in addition to demonstrating improvement in symptoms, including dysphagia[92–95](NCT03633617). Given these encouraging results as well as emerging real-world data[96], dupilumab was the first to receive FDA approval in May 2022 for the treatment of EoE. This has paved the way for a trial examining dupilumab for the treatment of EoG (NCT03678545).

Anti-IL-5

Reslizumab

Despite FA and EGID being driven by T_H2 signaling, they have very different clinical presentations, which could be due to FA being driven by responses from IL-5^- T_H2 cells whereas EGID are driven by IL-5^+ T_H2 cells[97]. Given the presumed role of eosinophils in EGID, a number of biologic agents that reduce eosinophils to varying degrees via the IL-5 pathway have been tested. In a cohort of 226 patients with moderate or severe EoE, neutralization of IL-5 with 1, 2, or 3 mg of reslizumab for 12 weeks reduced peak esophageal eosinophil counts by 59% ,67%, or 64%, respectively, compared to 24% in the placebo group by week 15; however there was no difference in physician EoE global assessment between treatment groups[98].

Mepolizumab

Similarly, IL-5 neutralization with mepolizumab subcutaneous injections for 12 weeks in a cohort of 59 EoE patients by Assa'ad et al reduced peak and mean eosinophils to less than 20 eos/hpf in 31.6% and 89.5% of subjects, respectively. However, no difference in EoE symptoms was observed after mepolizumab treatment[99]. Case studies of two severe adult asthmatics treated with mepolizumab, one with comorbid EoG and the other with EoN, exhibited improvement in their concurrent GI disease, but further study is required[87, 88]. An ongoing phase 2 clinical trial aims to enroll 16–75 year old patients (N=66) with EoE to assess the efficacy of 2 different doses of mepolizumab (NCT03656380).

Benralizumab

Another possible explanation for the lack of efficacy of reslizumab and mepolizumab is that they reduce, but do not deplete, eosinophils[100, 101]. A limited set of patients with hypereosinophilic syndrome involving gastrointestinal eosinophilia (N=7) received the anti-IL5RA antibody, benralizumab, in a phase 2 clinical trial[89]. All 7 patients had reduced gastrointestinal eosinophils, although 4 experienced disease flares while on therapy[102]. A trial of benralizumab for the treatment of PDGRFA-negative hypereosinophilic syndrome included 6 patients with concurrent gastric eosinophilia consistent with EoG, of whom 4 also had duodenal involvement. Peripheral blood and GI tissue eosinophils were depleted in each of these patients with a variable reduction in initial symptoms that returned in some with treatment reduction or diet liberalization[89]. Furthermore, an ongoing phase 3 clinical trial (NCT04543409) aims to recruit 12–65-year-old EoE patients (N=211) to test the efficacy of benralizumab recently released topline results where although treatment with

benralizumab showed improvement in histologic disease remission, it failed to improve symptoms of dysphagia compared to placebo[103].

In summary, biologics targeting eosinophils reduces eosinophilic inflammation in gastrointestinal tissues, but the persistence of symptoms suggests that eosinophils are only a part of the pathophysiology of EGIDs.

Anti-IgE

Omalizumab

In contrast to FA, omalizumab has not shown great success in EoE. In a cohort of 30 adults with EoE, omalizumab, given every 2–4 weeks for 16 weeks did not significantly reduce eosinophilic inflammation[104], consistent with non-IgE-mediated food reactions in most EoE patients. An early trial with omalizumab did not demonstrate improvement in tissue eosinophilia but did show a 42% reduction in absolute eosinophil count [86].

Anti-SIGLEC-8

Lirentelimab—The ENIGMA phase 2 clinical trial of lirentelimab, an eosinophil-depleting anti-Siglec-8 antibody, given monthly for 4 months at a low dose or high dose schedule demonstrated a dramatic reduction in gastrointestinal eosinophil counts and improvement in clinical symptoms in patients with EoG and eosinophilic duodenitis (EoD)[52]. The KRYPTOS phase 2/3 clinical trial of lirentelimab, in 276 subjects with EoE reported that 87.9% of high dose for 5 months and 92.5% of low dose treated subjects achieved the histologic endpoint of 6 or fewer eos/hpf compared to 10.9% of those receiving placebo. However, no associated symptomatic improvement was seen between groups, thus failing to meet the symptomatic co-primary endpoint[105]. These results add to a growing body of evidence suggesting that the pathogenesis of EGID involves mechanisms that are, at least partially, independent of eosinophilia, therefore biologics targeting eosinophils only may not alleviate the disease process.

Non T_H2-specific Inflammation Targets

Biologics used to treat inflammatory bowel disease have also been explored as a treatment for EoE in mainly small single-institution studies. Infliximab, an inhibitor of TNF-α, failed to reduce eosinophilic infiltration or resolve symptoms in three adults with severe corticosteroid-dependent EoE after 4–8 weeks of treatment[106]. Early studies on the α4β7 integrin inhibitor, vedolizumab, suggest that it may reduce dysphagia and esophageal eosinophilia in refractory EoG/EoN and in patients with concomitant Crohn's disease and symptomatic EoE, however more research is needed[90, 107, 108].

Upcoming novel biologics

Additional targets for biologics include the upstream alarmins: IL-25, IL-33, and TSLP (Figure 2). IL-33 was studied in a phase 2a study; 73% of peanut allergic adults tolerated 275 mg of peanut protein 15 days after a single infusion of the anti-IL-33 monoclonal antibody, etokimab, compared to 0% who received placebo[109]. A different anti-IL-33 biologic, itepekimab, has shown efficacy by improvement in lung function and asthma

control in a Phase 3 asthma study with and without combination therapy with dupilumab[110]. The anti-TSLP biologic, tezepelumab, has also shown promise in asthma (NAVIGATOR study)[111] and might have benefit in FA and EGID[112, 113].

Other clinical trials are also underway evaluating the co-stimulatory inhibitor abatacept (NCT04872218) in the treatment of peanut allergy. Looking beyond FA and EGIDs, several exciting Phase 1 and 2 clinical trials are studying novel biologics in AD, including ADX-914, a fully human anti-IL-7R antibody (NCT0550902); PF-07242813, a CD1a inhibitor (NCT04668066); and fezakinumab, an IL-22 inhibitor (NCT01941537). If these early investigations demonstrate safety and efficacy in AD, it is feasible that future studies will expand to other atopic diseases, including EoE and FA. Additional targets such as Th1 adjuvants added to allergens to induce a Th1-skewed response are being explored for FA and may be a potential target for allergic disease[114]. Other novel biologics being investigated include disruptive IgE inhibitors[115] and passive blockade with monoclonal antibodies to sIgE epitopes[116].

Conclusion

There is substantial mechanistic overlap between FA, asthma, AD, and EGIDs. Indeed, many biologics that are under investigation in FA and EoE were first studied in asthma or AD. Examples include omalizumab, which was first approved for asthma in 2003, and now being studied in food allergy, and dupilumab, which was first approved for atopic dermatitis in 2017 and only recently approved for EoE as well. Leveraging insights into mechanisms of action of these biologics in other atopic conditions will enable more precise identification of how biologics can play a role in FA and EGID and facilitate a more personalized targeted approach to therapy. More research is still needed to achieve this goal however, and some of the gaps in knowledge are noted in Table 3.

With the rapid advancement in knowledge in this area and further clinical trials underway, we also need to pay close attention to developing strategies to mitigate the impact of the high cost of biologics and reducing barriers to access for diverse patient populations. Home self-administration of many of these biologics may both improve access and reduce cost, but ensuring adherence with therapy and utilizing digital means of remote monitoring will be the key to continued success. With the plethora of biologics that will soon be available for use in FA and EGIDs, there is a great need for developing treatment algorithms that incorporate clinical presentation as well as biomarkers. Additionally, clinical practice guidelines developed by experts in the field through consensus building should differentiate between ill- and well-founded off-label practices to allow for the use of biologics pending regulatory approval. Although data integrity should not be compromised, biologics that are already approved in adults and have a track record of safety in children for other indications could be utilized for well-founded off-label practices through special access programs until full approval is available. Long-term studies are also critically important and will help identify durability and safety of these approaches. These strategies would allow physicians to better care for their pediatric and adult patients and bring severe disease under tighter control.

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Abbreviations

AD	Atopic dermatitis
AEs	Adverse events
CCR3	CC-chemokine receptor 3
EGF	Epidermal growth factor
EGIDs	Eosinophilic gastrointestinal disorders
EMR1	EGF module containing mucin-like hormone-like receptor 1
EoD	Eosinophilic duodenitis
EoG	Eosinophilic gastritis
EoEHSS	EoE histologic scoring system
EoN	Eosinophilic enteritis
eos/hpf	Eosinophils per high-power field
FA	Food allergy
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IL-4Rα	IL-4 receptor alpha
ILC2	Group 2 innate lymphoid cells
OIT	Oral immunotherapy
Siglec-8	Sialic acid-binding immunoglobulin-like lectin 8
SU	Sustained unresponsiveness
TCS	Topical corticosteroids
T_H2 cells	T helper 2 cells
TSLP	thymic stromal lymphopoietin

EoE	Eosinophilic esophagitis

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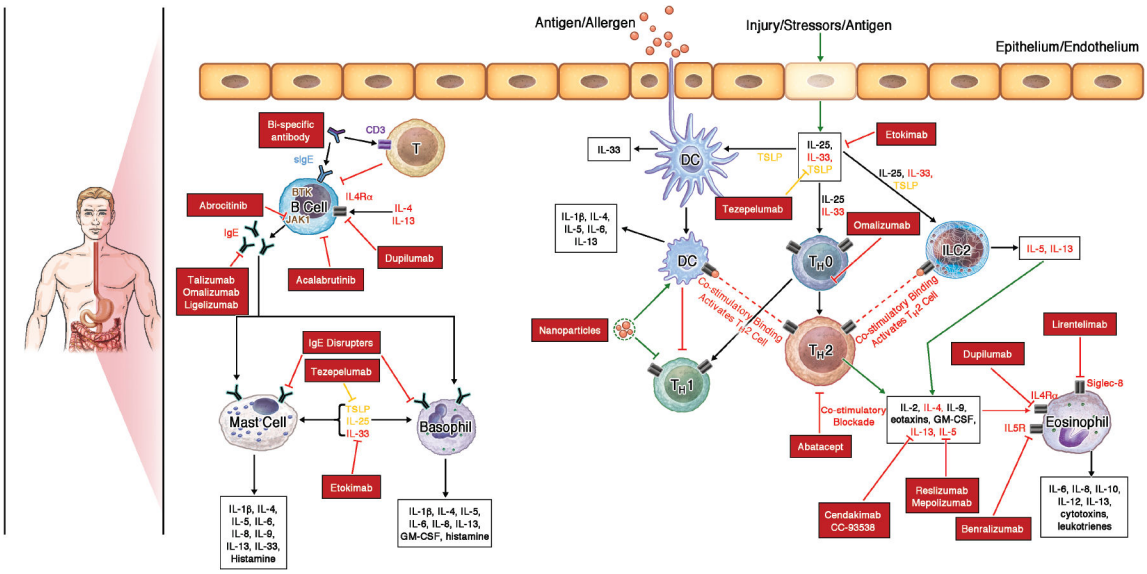

FIG1.

Biologics targeting key allergic pathways. Schematic of major allergic pathways that drive FA and EGIDs highlighting pathways that are targeted by biologics (red boxes) to treat these diseases.

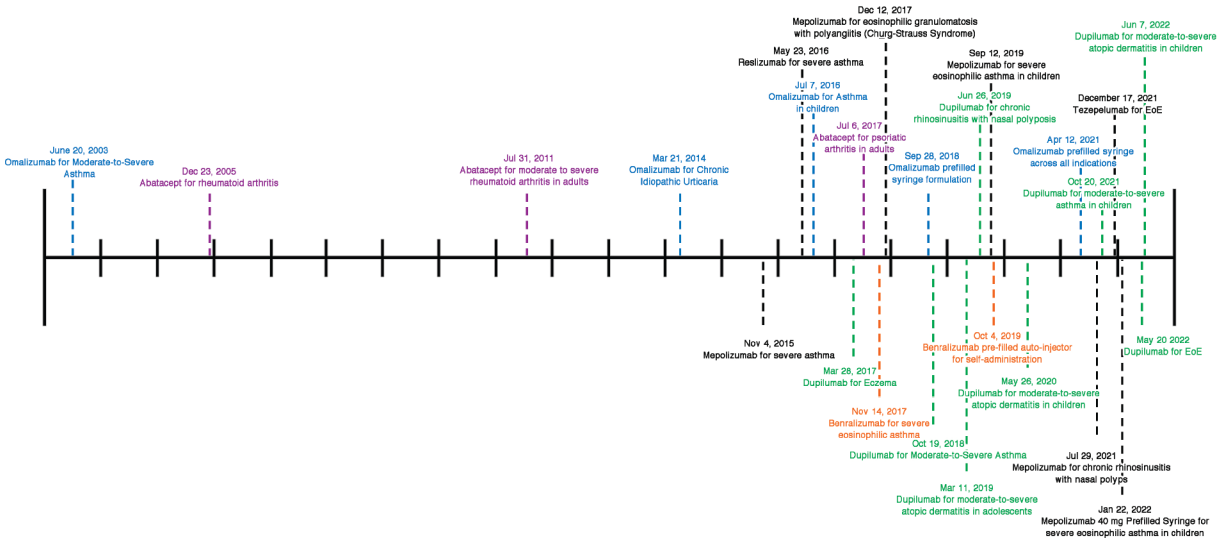

FIG2.

FDA approval of biologics that are used or are under investigation for the treatment of FA and/or EGIDs. Most biologics being investigated for use in FA and/or EGIDs have been approved for use in other atopic diseases. Recent years have seen an explosion of FDA approvals for the use of these biologics for several different diseases. Each tick in the timeline represents 1 year.

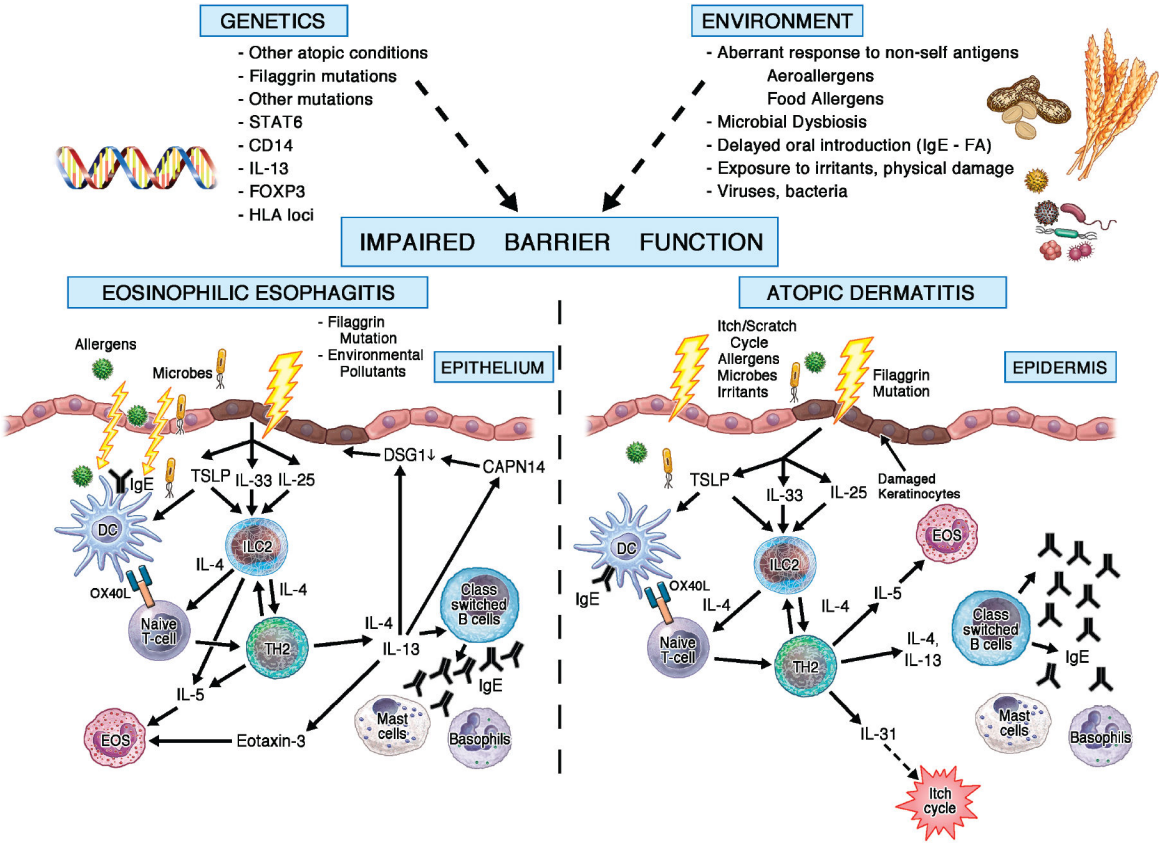

FIG3.

Impaired skin barrier in EoE and AD. Several genetic and environmental factors lead to the disruption of the epithelial skin barrier. This disrupted barrier initiates downstream signaling pathways that drive EoE and AD.

Table 1.

Ongoing clinical trials in FA.

Intervention			Trial Number(s)	Phase	Population	Primary Endpoint
Biologic agents in food allergy	Anti-IgE	Omalizumab	NCT04037176 NCT03964051	IV	6–18 yo with allergy to 1 or more foods 18–70 yo with food allergy	Change in challenge threshold after 18 weeks or 3 months of treatment in patients treated with Omalizumab versus placebo.
		Omalizumab + peanut OIT	NCT01781637	II	7–25 yo with peanut allergy	Tolerance of 2000 mg 6 Weeks After Last Dose of Omalizumab/ Placebo [Time Frame: 6 weeks after last dose of omalizumab/ placebo]
		Omalizumab +/− multi-allergen OIT	NCT03881696	III	1–56 yo with peanut allergy + 2 additional food allergies (milk, egg, wheat, cashew, hazelnut, walnut)	Number of participants to successfully consume a single dose of ≥ 600 mg of peanut protein. [Time Frame: During the DBPCFC at the end of Stage 1: 16 to 20 weeks after Stage 1 treatment initiation]
		Omalizumab + multi-allergen OIT	NCT04045301	IIb	6–25 yo with multi-food allergy (≥3 foods)	Efficacy of omalizumab at decreasing time-to-maintenance (1500mg total protein) [Time Frame: 52 weeks)
		Ligelizumab	NCT04984876	III	6–55 yo with peanut allergy	Proportion of participants to tolerate a single dose of ≥ 600 mg of peanut protein at week 12. [Time Frame: 12 weeks]
	Anti-IL4Rα	Dupilumab	NCT03793608 NCT04148352	II	6–17 yo with peanut allergy 4–50 yo with cow's milk allergy	Proportion of patients treated with dupilumab monotherapy that pass DBPCFC with peanut protein. [Time Frame: week 24) Proportion of subjects treated with dupilumab plus milk protein OIT vs placebo plus milk protein OIT who tolerate at least 2040 mg (cumulative) cow's milk protein during DBPCFC to milk at week 18 [Time Frame: Week 18]
		Dupilumab + AR101 (peanut oral immunotherapy)	NCT03682770	II	6–17 yo with peanut allergy	Proportion of patients who successfully complete an exit food challenge with 2044 mg cumulative peanut protein. [Time Frame: Up to 40 weeks].
	Anti-IgE + Anti-IL4Rα	Omalizumab + dupilumab +/− multi-allergen OIT	NCT03679676	II	5–55 yo with peanut allergy + 1–2 other food allergies	The success rates of passing a FC to peanut and two other FAs [Time Frame: 44 weeks]
	Anti-JAK	Abrocitinib	NCT05069831	I	18–50 yo with food allergy	Change in skin prick and basophil activation tests. [Time Frame: baseline and after 4 months of treatment].
	Anti-BTK	Acalabrutinab	NCT05038904	II	18+ yo with peanut or tree nut allergy	Change in the highest dose of peanut or tree nut that is tolerated during oral food challenge before and after taking acalabrutinib, as defined by the PRACTALL consensus grading system. [Time Frame: Baseline and Day 2].
	co-stimulatory inhibitor	Abatacept	NCT04872218	II	14–50 yo with peanut allergy	Peanut specific/total IgE at week 24 [Time Frame: 24 weeks]

Table 2.

Ongoing clinical trials in EGID.

Intervention			Trial Number(s)	Phase	Population	Primary Endpoint
Biologic agents in eosinophilic gastrointestinal disorders	S1P receptor modulator	Etrasimod*	NCT04682639	II	18–65 yo with eosinophilic esophagitis	Percent Change From Baseline in Esophageal Peak Eosinophil Count (PEC) [Time Frame: Baseline to Week 16]
	Anti-IL5	Mepolizumab	NCT03656380	II	16–75 yo with EoE	Mean Change in Dysphagia from Baseline to 3 months Post-treatment [Time Frame: Baseline, Month 3 Post-Treatment]
	Anti-IL5Rα	Benralizumab	NCT04543409 NCT05251909	III	12–65 yo with eosinophilic esophagitis 12–130 yo with Eosinophilic Gastritis and/or Gastroenteritis	Proportion of patients with a histologic response at Week 24, defined as a peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf. [Time Frame: Week 24] Proportion of patients achieving a histological response in the stomach and/or in the duodenum [Time Frame: Week 24]
	Anti-IL-13	CC-93538	NCT05175352 NCT04753697	I II	18–75 yo with eosinophilic esophagitis 12–75 yo with eosinophilic esophagitis	Pharmacokinetics [Time Frame: Up to 18 Weeks] Change in dysphagia days clinical response [Time Frame: At week 24]
		CC-93538	NCT04991935 NCT05214768	III	12–75 with eosinophilic esophagitis 12–75 yo with eosinophilic gastroenteritis	Incidence of Adverse Events (AEs) [Time Frame: For a minimum of 28 months] Changes in mean number of peak eosinophils (eos) per high-power field (hpf) in gastrointestinal (GI) biopsies from baseline to Week 16 [Time Frame: At Week 16]
	Anti-IL4Rα	Dupilumab	NCT03678545 NCT04394351 NCT05247866	II III IV	12–70 yo with Eosinophilic Gastritis 1–11 yo with eosinophilic esophagitis 6–25 yo with eosinophilic esophagitis	Relative change of peak eosinophil counts in the stomach [Time Frame: 12 weeks] Proportion of patients achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf (400×) [Time Frame: Week 16] Esophageal Eosinophilia (number of eosinophils in the esophagus) [Time Frame: up to week 48]
	Anti-Siglec-8	Lirentelimab	NCT03664960 NCT04322708 NCT05152563 NCT04322604 NCT04620811 NCT04856891	II II/III III	18–80 yo with Eosinophilic Gastritis and/or Eosinophilic Duodenitis 12–80 yo with eosinophilic esophagitis 18–80 yo with Eosinophilic Gastritis and/or Eosinophilic Duodenitis 18–80 yo with Eosinophilic Duodenitis	The safety and tolerability of AK002 by evaluating adverse events assessed using the CTCAE version 4.03 [Time Frame: Day 785 (End of Study)] The proportion of patients who achieve esophageal intraepithelial eosinophil count of ≤6 eosinophils/hpf [Time Frame: At Week 24] Proportion of Responders as determined by gastric or duodenal tissue eosinophil counts. [Time Frame: At Week 24] The safety and tolerability of lirentelimab by evaluating adverse events assessed using the CTCAE version 5.0 [Time Frame: Day 561 (End of Study)] Proportion of Responders, where a responder is a patient achieving a

Intervention			Trial Number(s)	Phase	Population	Primary Endpoint
						mean peak duodenal eosinophil count ≤15 cells/3 duodenal hpf. [Time Frame: At Week 24]
	Anti-IL15	CALY-002*	NCT04593251	I	18–50 yo with either eosinophilic esophagitis or celiac disease	Incidence of treatment-emergent adverse event [Time Frame: through study completion, an average of 3 months post last dose]

Table 3.

Gaps in knowledge for the use of biologics in FA and EGID.

Remaining questions	Steps moving forward
What is the optimal dose and timing of the biologic?	Inclusion of different arms with different doses or timecourses for the biologic.
How effective are these biologics in comparison with each other?	Design clinical trials aimed at comparing the efficacy of different biologics either individually or in combination.
How can we track the effectiveness of a biologic?	Identification of biomarkers for clinical response to the biologic through application of omics technology at various timepoints throughout treatment: pre-treatment, during treatment, and post treatment.
How do we identify which biologic is best suited for a food allergic individual?	Identification of baseline biomarkers suggestive of optimal response to specific biologics.
Would using these biologics in combination with each other increase their effectiveness?	Incentivize research investigating combination therapies.
How durable are the benefits of these biologics?	Long-term follow-up from completed studies can assess how long these benefits last post-study completion and screen for the potential of long-term adverse events.