

Biologic Therapies for Immunoglobulin E-mediated Food Allergy and Eosinophilic Esophagitis



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KEYWORDS

• Food allergy • Eosinophilic esophagitis • Anti-IgE • Anti-IL-5 • Anti-IL-13 • QAX576 • OC000459

KEY POINTS

- Immunoglobulin (Ig) E-mediated food allergy and eosinophilic esophagitis (EoE) are chronic, allergen-mediated disorders.
- Investigation of biologic therapies in IgE-mediated food allergy and EoE have provided insights into the pathophysiology and treatment of these disorders.
- In IgE-mediated food allergy, anti-IgE therapy seems to increase tolerability of food allergens and safety of oral desensitization protocols, although further larger studies are necessary to further elucidate the most safe and effective use of anti-IgE.
- In EoE, the use of biologics targeting interleukin (IL)-5, IL-13, IgE, and the CRTH2 receptors, have had mixed results. Decreases in esophageal eosinophilia were not necessarily accompanied by symptomatic remission.
- Identification of EoE phenotypes that are responsive to biologics and investigation of biologics in combination with other therapies may help elucidate a role for biologic therapy in EoE.

INTRODUCTION

Food allergy is defined as an aberrant immune response to food proteins leading to mucocutaneous, gastrointestinal, and/or respiratory symptoms. Food allergy can encompass purely IgE-mediated food allergy as well as mixed IgE-mediated and non-IgE-mediated disease, such as eosinophilic esophagitis (EoE).¹ The development

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and investigation of biologics for the treatment of IgE-mediated food allergy and EoE have provided further insight into the pathophysiology and management of these disorders. This article provides an overview of biologic therapies that are being investigated or have potential as treatments for IgE-mediated food allergy and EoE.

IMMUNOGLOBULIN E-MEDIATED FOOD ALLERGY

The prevalence of food allergy has been estimated at 8% in children and 5% in adults.² Although the incidence of food allergy continues to increase,³ allergen avoidance and treatment of accidental ingestion with epinephrine remain the only US Food and Drug Administration (FDA)-approved treatments.⁴ Allergen avoidance and fear of accidental ingestion are associated with stress and anxiety that significantly impair quality of life for affected children and their caregivers.⁵

Food allergen immunotherapy via oral, sublingual, and epicutaneous routes is being actively investigated as a treatment of IgE-mediated food allergy. Gradually increasing exposure to food allergens can lead to desensitization and induce immune tolerance to food allergens. The safety and efficacy of immunotherapy for food allergy remain unclear, because adverse reactions can occur and tolerance has been shown to wane after active immunotherapy is discontinued.^{6,7}

Anti-Immunoglobulin E for Immunoglobulin E-Mediated Food Allergy

IgE-mediated food allergy reactions occur when mast cells and basophils are activated after allergen exposure through cross-linking of preformed allergen-specific IgE on the cell surface.⁸ Anti-IgE is under investigation both as a stand-alone therapy and an adjunctive treatment that could potentially improve the safety and efficacy of allergen immunotherapy (Table 1).

Omalizumab

Omalizumab (Xolair; Genentech, South San Francisco, CA) is a humanized IgG₁ monoclonal antibody (mAb) that binds the Fc region of IgE and blocks the binding of IgE to its high-affinity FcεRI on mast cells, basophils, and dendritic cells, thereby interrupting the allergic cascade.¹⁸ It is administered subcutaneously and is FDA approved for moderate to severe persistent allergic asthma inadequately controlled with inhaled corticosteroids in patients 12 years of age or older.¹⁹ Omalizumab is also FDA approved for chronic idiopathic urticaria inadequately controlled with H1 antihistamines in patients 12 years of age or older.²⁰

For allergic asthma, dosing is calculated based on pretreatment serum IgE levels and body weight, with dosages ranging between 150 to 375 mg administered subcutaneously every 2 to 4 weeks.¹⁹ For chronic idiopathic urticaria, the dosage is between 150 to 300 mg administered subcutaneously every 4 weeks, independent of serum IgE level or body weight.²⁰

Omalizumab can exert several biological effects in allergic disease. It can significantly reduce FcεRI expression on basophils and plasmacytoid dendritic cells,^{21–24} decrease serum IgE levels,^{25,26} and decrease allergen-specific basophil reactivity²⁷ and histamine release.^{28,29} It has been investigated both as a stand-alone and adjunctive therapy to allergen immunotherapy in allergic rhinitis and as a therapy for atopic dermatitis, with mixed results.²⁰

Talizumab

Talizumab (TNX-901; Tanox, Houston, TX) is a humanized IgG₁ mAb administered subcutaneously. Like omalizumab, talizumab binds the Fc region of IgE, blocking IgE binding to FcεRI.¹⁸

Table 1

Published clinical trials and case series investigating anti-immunoglobulin E as a therapy for immunoglobulin E-mediated food allergy

First Author, Year	Allergen	Patient Groups	Design/Doses	Clinical Results	AEs
OMA as Stand-alone Therapy to Improve Food Allergy Tolerance					
Leung et al, ⁹ 2003	Peanut	Placebo (n = 23) 150 mg (n = 19) 300 mg (n = 19) 450 mg (n = 19)	Randomized, double-blind, placebo-controlled, dose- ranging Age: 13–59 y Screening: DBPCFC Drug: 150 mg, 300 mg, or 450 mg of TNX-901 or placebo SQ every 4 wk for 4 doses OFC: 2–4 wk after the fourth dose of TNX-901 or placebo	Clinical results: Increase from baseline in the mean threshold dose that induced hypersensitivity to peanut flour: increase of 2627 mg in the group given 450 mg of TNX-901 ($P < .001$) Immune changes: Significant decreases in serum IgE levels at all 3 dosing levels compared with placebo	Number of systemic AEs (45–50 per group) and number of patients who had AEs (15–19 per group) similar among the 4 groups Diarrhea, nausea, vomiting, fatigue, fever, food allergy unrelated to OFC, upper respiratory tract infection, headache, arthralgia
Rafi et al, ¹⁰ 2010	Fish Shellfish Peanut Tree Nuts Egg Soybean Wheat Multiple other	22 patients with persistent asthma and IgE-mediated food allergy	Prospective pilot Age: 4–66 y Drug: OMA 150–300 mg every 2–4 wk for 6 doses	Clinical results: Decreases (improvements) in food- induced symptoms (atopic dermatitis, n = 8; lower respiratory symptoms, n = 13; upper respiratory symptoms, n = 8; urticaria, n = 3; angioedema, n = 9)	No AE caused by OMA use

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Table 1
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First Author, Year	Allergen	Patient Groups	Design/Doses	Clinical Results	AEs
Sampson et al, ¹¹ 2011	Peanut	Placebo (n = 5) OMA (n = 9)	Multicenter, randomized, double-blind, placebo- controlled, parallel-group Age: Placebo, mean 26.6 y; OMA, mean 16.3 y Screening: DBPCFC Drug: placebo or OMA (minimum of 0.016 IU/mL every 4 wk; doses >300 mg received divided dose every 2 wk) for 24 wk Week 24: second double-blind OFC	Clinical results: 4 (44.4%) OMA- treated subjects vs 1 (20%) placebo-treated subject tolerated ≥ 1000 mg peanut flour during OFC after 24 wk of treatment with study drug ($P = .324$)	Study stopped early because of severity of 2 anaphylactic reactions during screening OFCs
Savage et al, ¹² 2012	Peanut	n = 14	6-mo open-label study Age: 18–44 y 6 mo of OMA OFC1 during screening OFC2 between weeks 2–8 once Pn-BHR (decreased to <20% baseline) OFC 3 at 6 mo	Clinical results: OFC2: significant increase in the threshold dose of peanut inducing allergic symptoms (80–6500 mg, $P < .01$); OFC3: no further increases in the OFC threshold dose Immune changes: By week 8 of OMA therapy, 5 patients had near-complete suppression of Pn-BHR and 9 patients had a 10-fold increase in the amount of allergen required to achieve maximal BHR	—

OMA as Adjunctive Therapy to Increase Safety of Desensitization

Nadeau et al, ¹³ 2011; Bedoret et al, ¹⁴ 2012	CM	n = 11	Pilot study Age: 7–17 y CM OIT performed in combination with 16 wk of OMA OMA treatment started at week 0, and CM OIT started at week 9 DBPCFC performed 8 wk later (week 24 of the study)	Clinical results: 9 of 10 subjects reached the maximum daily dose of 2000 mg milk (the primary end point of the study). 9 patients who had reached a daily dose of 2000 mg passed DBPCFC and open challenge. 9 patients continued with daily milk ingestion >8000 mg daily Immune changes: Post-hoc subanalysis of blood drawn at weeks 0, 9, 10, 12, 14, 16, 24, 30, 36, and 52 in 5 subjects. Decrease in milk-specific CD4+ T-cell proliferation 1 wk into desensitization protocol. Milk-specific CD4+ T-cell proliferation returned with shift from IL-4 to IFN-γ production, whereas the subjects remained on high doses of daily oral milk over the following 3 mo. Decrease in milk-specific IgE and a 15-fold increase in milk-specific IgG4	One subject voluntarily discontinued the study because of abdominal migraines 2 reactions required epinephrine
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Table 1
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First Author, Year	Allergen	Patient Groups	Design/Doses	Clinical Results	AEs
Schneider et al, ¹⁵ 2013	Peanut	n = 13	Age: 8–15 y Week 0–12: pretreatment with OMA Week 12: initiation of oral desensitization (11 doses of 0.1, 0.5, 1.5, 3, 7, 15, 30, 60, 125, 250, and 500 mg; cumulative dose, 992 mg peanut flour; administered over 6 h) Week 12–20: weekly increase in the daily oral dose to 4000 mg peanut flour (750, 1000, 1250, 1600, 2000, 2600, 3250, and 4000 mg) Week 20: OMA discontinued after subjects reached 4000 mg daily dose. Daily peanut dosing continued Week 30–32: DBPCFC followed by open peanut challenge (8000 mg)	Clinical results: 13 subjects tolerated initial desensitization on the first day (maximum dose, 500 mg peanut flour; cumulative dose, 992 mg). 12 subjects reached maximum maintenance dose of 4000 mg peanut flour per day in a median time of 8 wk. 12 subjects continued 4000 mg peanut flour daily dosing and subsequently tolerated OFC with 8000 mg peanut flour (about 20 peanuts)	Total of 72 reactions during the study First day of desensitization: 6 of 13 grade 1 allergic reactions requiring no treatment or antihistamines Up-dosing phase: 1 of 13 with history of supraventricular tachycardia required epinephrine for nausea, light-headedness, hypersalivation after a 1250-mg dose. 1 of 13 withdrew from study because of persistent nausea, vomiting, and hypersalivation after reaching 1250-mg dose. 6-mo maintenance phase: 1 of 13 required epinephrine for vomiting, diarrhea, and wheezing. 1 of 13 received epinephrine 3 times for coughing, hives, and wheezing (possibly food-dependent exercise-induced anaphylaxis) and withdraw from study

Wood et al, ¹⁶ 2016	CM	n = 57	Randomized, double-blind, placebo-controlled Age: 7–32 y Screening DBPCFC with 2 g milk First 16 mo: Treatment with OMA or placebo After 4 mo of study drug: Open-label MOIT initiated with escalation to maintenance over 22–40 wk to at least 520 mg (goal 3800 mg), followed by daily maintenance dosing through month 28 Month 16: treatment unblinded; OMA continued for 12 mo; placebo injections discontinued Month 28: OMA discontinued, patients underwent 10 g OFC Month 28–32: subjects who passed OFC continued milk maintenance dose for 8 wk and then stopped milk OIT for 8 wk Month 32: rechallenge with 10 g OFC to assess sustained unresponsiveness	Clinical results: No significant differences in subjects who passed 10 g desensitization OFC (88.9% in OMA group vs 71.5% in placebo-treated group) or achieved SU (48.1% in the OMA group vs 35.7% in the placebo group) Immune changes: Milk and casein IgE levels significantly increased in OMA group and significantly reduced in placebo group at month 4. Casein and β-lactoglobulin IgG4 levels, IgG levels, and IgG4/IgE ratios increased in both OMA and placebo groups. Basophil activation to milk stimulation lower in the OMA group compared with placebo	Percentage of symptom-free doses during escalation significantly greater in OMA group compared with placebo (91.5% vs 73.9%; $P < .0001$). Median dose-related reactions requiring treatment significantly fewer in OMA group (0.0% vs 3.8% of doses per subject; $P = .0008$). Severity grade of allergic reactions significantly milder in OMA group (mild: median, 0.5% vs 7.9% doses per subject, $P = .0001$; moderate: median, 0.0% vs 0.5% doses per subject, $P = .0005$)
Martorell-Calatayud et al, ¹⁷ 2016	CM Egg	CM (n = 5) Egg (n = 9)	Case series Age: 3–13 y CM or egg OIT with OMA given as pretreatment for 9 wk and in conjunction with OIT until 2 mo after the maintenance dose was reached (6.6 g milk, 1.8 g egg)	Patients who could not tolerate the same OIT protocol without OMA were able to reach goal maintenance dose with OMA as pretreatment and concurrent therapy	4 patients (28%) developed mild allergic reactions during the induction phase of OIT

Abbreviations: AE, adverse events; BHR, basophil histamine release; CM, cow's milk; DBPCFC, double-blind placebo-controlled food challenge; IFN, interferon; OFC, oral food challenge; OIT, oral immunotherapy; OMA, omalizumab; Pn-BHR, peanut-induced basophil histamine release; SQ, subcutaneous; TNX-901, talizumab.

Clinical Trials in Food Allergy

Anti-immunoglobulin E as stand-alone therapy to decrease food allergy symptoms
Leung and colleagues, 2003 The first trial of anti-IgE for treatment of food allergy was performed with talizumab in 2003.⁹ This randomized, double-blind, placebo-controlled, dose-ranging study included 84 patients aged 12 to 60 years with a history of immediate hypersensitivity to peanut, total serum IgE levels between 30 and 1000 IU/mL, a positive SPT to peanut, and reactivity to peanut confirmed by a double-blind, placebo-controlled oral food challenge (DBPCFC). These patients were randomly assigned to talizumab (150, 300, or 450 mg) or placebo subcutaneously every 4 weeks for 4 doses. All 3 dosages increased the threshold of reactivity to peanut during an oral food challenge performed 2 to 4 weeks after the last administered dose of anti-IgE. This change was statistically significant in the group receiving the highest dose of talizumab. In this 450-mg dose group, the threshold increased from 178 mg of peanut (approximately one-half of a peanut) to 2805 mg (almost 9 peanuts).

Talizumab was taken off the market because of legal difficulties, and subsequent studies with anti-IgE in IgE-mediated food allergy have been performed with omalizumab.

Rafi and colleagues, 2010 This publication reported that 22 patients treated with omalizumab for allergic asthma with concomitant food allergy (history of allergic food reaction and skin prick test positive to food) had decreased or absent clinical symptoms on accidental or intentional (but not medically recommended) ingestion.¹⁰ These clinical improvements were seen by the sixth dose of omalizumab. The reported improvements in food-induced symptoms (atopic dermatitis, $n = 8$; lower respiratory symptoms, $n = 13$; upper respiratory symptoms, $n = 8$; urticaria, $n = 3$; angioedema, $n = 9$) and doses of ingested food were variable, making the results subject to interpretation.

Sampson and colleagues, 2011 A phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial investigated whether omalizumab (at a dose of 0.016 mg/kg/IgE) would be effective, similar to talizumab, at preventing allergic reactions after peanut ingestion in peanut-allergic children 6 years of age or older.¹¹ The study was stopped early because of the severity of 2 anaphylactic reactions that occurred during the screening oral food challenges. Therefore, only 14 subjects reached the primary end point of DBPCFC after treatment with the study drug omalizumab or placebo. However, even the limited data suggested an increase in tolerability to peanut with omalizumab: 44% (4 out of 9) of the omalizumab-treated subjects compared with 20% (1 out of 5) of the placebo-treated subjects were able to tolerate greater than or equal to 1000 mg of peanut flour during an oral food challenge after 24 weeks of treatment.

Savage and colleagues, 2012 A 6-month open-label study showed that the mean tolerated dose of peanut protein increased from 80 mg to 6500 mg after 2 to 8 weeks and 5080 mg after 6 months of omalizumab therapy in 14 subjects with peanut allergy.¹² By week 8 of omalizumab therapy, 5 patients had near-complete suppression of peanut-induced basophil histamine release and 9 patients had a 10-fold increase in the amount of allergen required to achieve maximal basophil histamine release.

Taken together, these data suggest the possibility of using anti-IgE as a means to increase threshold tolerance levels and offer a degree of protection for patients in cases of accidental ingestions.

Anti-immunoglobulin E as an adjunctive therapy for oral immunotherapy

Omalizumab has also been investigated as a potential adjunctive therapy that could decrease the immediate adverse reactions that occur during oral immunotherapy (OIT) and possibly enhance the development of tolerance.

Nadeau and colleagues, 2011 In the first study of omalizumab in combination with OIT, omalizumab seemed to be safe and efficacious at enhancing the development of tolerance. In this pilot, phase I study, 11 children (7–17 years of age) with cow's milk allergy were pretreated with omalizumab for 9 weeks before undergoing rush desensitization to milk.¹³ Oral milk doses were increased from 0.1 to 1000 mg over 6 hours and then to 2000 mg over 7 to 11 weeks. Subjects remained on omalizumab throughout the dose escalation phase. One subject discontinued the study because of nonallergic abdominal migraines. Of the remaining 10 patients, 9 reached the maximum daily dose of 2000 mg of milk and passed a DBPCFC (cumulative dose of 7250 mg, or 220 mL, of milk) and an additional open challenge of 4000 mg (120 mL) of milk. The tenth patient tolerated a maximum dose of 500 mg of milk during the DBPCFC (total cumulative dose, 1000 mg, 30 mL). All patients in the study experienced allergic reactions, although most were mild and did not require treatment. One subject required epinephrine for rhinitis and urticaria after the 1000-mg dose of rush desensitization. Two other subjects received epinephrine at home by their caregivers during the maintenance phase, one for upper lip swelling and urticaria on the left leg, and one for urticaria on the right arm. There were no adverse reactions reported to the omalizumab injections.

Bedoret and colleagues, 2012 A post-hoc analysis of 5 patients who were enrolled in this study showed a marked decrease in milk-specific CD4+ T-cell proliferation 1 week after initiation of desensitization.¹⁴ This decrease persisted during the dose escalation phase. However, milk-specific CD4+ T-cell proliferation subsequently returned while patients remained on daily oral milk. T-regulatory cells did not seem to be involved in the reduction of milk-specific CD4+ T-cell proliferation. Rather, anergy of the milk-specific CD4+ T cells was implicated as a possible explanation.

Schneider and colleagues, 2013 Omalizumab was also shown to possibly be safe and efficacious as an adjunctive treatment to facilitate rapid and successful oral desensitization in peanut allergy.¹⁵ Thirteen patients with peanut allergy were treated with omalizumab for 12 weeks before starting OIT with peanut. All patients were able to reach a dose of 500 mg of peanut on the first day (cumulative dose of 992 mg). Twelve patients were able to reach the maintenance dose of 4000 mg of peanut, after which omalizumab treatment was discontinued. These patients were able to tolerate a cumulative dose of 8000 mg of peanut flour during a DBPCFC or an open challenge greater than or equal to 12 weeks after omalizumab was discontinued. In terms of safety, there were 2 patients who received epinephrine at home during the maintenance phase. One patient received epinephrine for vomiting, diarrhea, and wheezing that occurred 2.5 hours after peanut dosing. The other patient received epinephrine 3 times for coughing, hives, and wheezing, for what could have been food-dependent exercise-induced anaphylaxis.

Wood and colleagues, 2016 The first double-blind placebo-controlled trial comparing omalizumab with placebo as adjunctive therapy for cow's milk OIT in 57 subjects with severe milk allergy was recently published.¹⁶ Patients received 4 months of omalizumab or placebo pretreatment before initiation and dose escalation of milk OIT over 22 to 40 weeks followed by a maintenance phase through month 28, after which omalizumab/placebo was discontinued. Patients who passed an oral food challenge at month 28 continued maintenance dosing for 8 weeks, followed by a period of discontinuation before rechallenge at month 32 to assess sustained unresponsiveness. There was no difference in rates of desensitization (proportion of patients who passed a 10-g oral food challenge at month 28) or sustained unresponsiveness (proportion of

patients who passed the rechallenge at month 32). However, there were significantly fewer adverse reactions during dose escalation and fewer doses were required to achieve maintenance in the omalizumab-treated subjects. Significantly fewer reactions requiring epinephrine occurred in the omalizumab-treated group (2 doses in the omalizumab-treated group vs 18 doses in the placebo-treated group). This finding suggests that the primary advantage of omalizumab possibly lies in its ability to significantly improve the safety of OIT.

Martorell-Calatayud et al, 2016 Subsequently, a case series was published of 14 egg-allergic and cow's milk-allergic patients who had previously failed OIT because of grade 3 to 4 allergic reactions, but were able to tolerate OIT with only mild allergic reactions when omalizumab was given as pretreatment for 9 weeks and in conjunction with OIT until 2 months after the maintenance dose was reached.¹⁷

Summary

Omalizumab has been trialed as a stand-alone therapy to decrease food allergy symptoms and as an adjunct therapy in OIT trials. Initial results suggested that omalizumab increased tolerability of peanut in peanut-allergic patients^{11,12} and possibly increased tolerability of OIT in peanut-allergic and cow's milk-allergic patients.^{13,15} The most recent double-blind placebo-controlled trial for omalizumab with OIT suggests that omalizumab may allow for safer desensitization by increasing the tolerance threshold, although it may not affect efficacy outcomes such as desensitization and sustained unresponsiveness.¹⁶ Further information is needed about safety issues surrounding the use of omalizumab with OIT because allergic reactions requiring the use of epinephrine still occurred during these trials. Larger studies evaluating omalizumab with OIT for peanut allergy are currently ongoing.⁷

EOSINOPHILIC ESOPHAGITIS

EoE is a chronic, antigen-mediated immune disease characterized by esophageal remodeling and dysmotility leading to food impactions and strictures and symptoms of chronic pain, feeding intolerance, and dysphagia. Diagnostic criteria are esophageal eosinophilia of greater than or equal to 15 eosinophils per high-power field (HPF) despite adequate acid blockade with proton pump inhibitor therapy.

Successful therapeutic interventions in patients with EoE include elimination diets, topical steroids, and amino acid.³⁰

The T_H2 pathway has been implicated in EoE pathogenesis. As such, biologic therapies targeting IL-5, IL-13, and IgE have been investigated as potential treatments for EoE. The results of these studies and other potential biologic agents that could be useful for EoE treatment are reviewed later ([Table 2](#)).

Anti-Interleukin-5

IL-5 has a critical role in eosinophil expansion, differentiation, activation, migration, and tissue survival.⁴³ Antibodies targeting the cytokine IL-5 (mepolizumab, reslizumab) or the IL-5 receptor (benralizumab) have been developed. Out of the developed anti-IL-5 therapies, mepolizumab has been investigated most extensively as a treatment of various allergic and/or eosinophil-driven disorders, including asthma, atopic dermatitis, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and nasal polyposis.^{44–52}

In severe asthmatics with blood and sputum eosinophilia, mepolizumab was shown to decrease peripheral eosinophilia, reduce the number of clinically significant exacerbations, improve forced expiratory volume in 1 second (FEV₁) before and after

Table 2
Summary of clinical trials and studies investigating the use of biologics as potential treatment of eosinophilic esophagitis

First Author, Year	Study Design and Dose	Follow-up EGD* (wk)	Age (y)	Patient Groups	Clinical Results	Immune Changes	Adverse Events
Mepolizumab							
Stein et al, ³¹ 2006	Open-label phase I/II safety and efficacy study 10 mg/kg (maximum, 750 mg) at week 8, 12, and 16	8 and 20	18–41	n = 4	Improvement of SF-36 quality-of-life scores ($P = .03$)	Significant decrease in blood eosinophil counts and percentage of CCR3+ cells Significant decrease in mean, median, and maximum esophageal eosinophil counts	Mild, including headache, URI symptoms, and 1 episode of hypotension
Stein et al, ³² 2008	Open-label phase I/II 10 mg/kg (maximum, 750 mg) at week 8, 12, and 16 Cohort A (n = 14): No change in immunosuppressant or antieosinophil medications Cohort B (n = 6): Decrease immunosuppressant or antieosinophil medications by 25% after the second mepolizumab infusion at week 12 Cohort C (n = 5): Decrease immunosuppressant or antieosinophil medications by 50% after the second mepolizumab infusion at week 12	Blood drawn at weeks 8 and 20	18–57	HES (n = 18) EoE (n = 6) EGID (n = 1)	—	Decreased blood eosinophil counts in 23 of 25 subjects Decreased percentage of CCR3+ cells Increased IL-5R α expressed in eosinophils Increased number of IL-5 producing CD8+ cells	Mild, including headache, and 1 episode of hypotension

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First Author, Year	Study Design and Dose	Follow-up EGD* (wk)	Age (y)	Patient Groups	Clinical Results	Immune Changes	Adverse Events
Straumann et al, ³³ 2010	Randomized, double- blind, placebo- controlled phase I/II 750 mg at weeks 0 and 1 Nonresponders by week 4 also received 1500 mg at weeks 5 and 9	4 and 13	M: mean 32 P: mean 34	M (n = 5) P (n = 6)	M: >20% improvement in proportion of days subjects reported dysphagia between weeks 9 and 13, which increased up to ~30% compared with baseline between weeks 13 and 17 P: 20% and 18%, respectively	Following changes seen after treatment in M group but not P group: 1. Decreased peak and mean esophageal eosinophil counts, although primary end point (<5 eosinophils per HPF) was not met 2. Decreased blood eosinophil counts 3. Decreased extracel- lular EDN deposition in the esophagus 4. Decreased esopha- geal EDN-positive eosinophils, eotaxin-1 positive cells, eotaxin-2 positive cells, eotaxin-3 positive eosinophils, IL-5-positive cells 5. Decreased TGFβ1 and tenascin C expression by epithelial cells 6. Decreased blood ECP and EDN levels	Mild, including fatigue, URI symptoms

Conus et al, ³⁴ 2009	Subanalysis of Straumann 2010 ³³	4 and 13	M: mean 32 P: mean 34	M (n = 5) P (n = 6)	—	No changes in IL-5R α expressed in eosinophils	—
Conus et al, ³⁵ 2010	Post-hoc analysis of Straumann 2010	4 and 13	M: mean 32 P: mean 34	M (n = 5) P (n = 6)	—	Mepolizumab did not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa	—
Assa'ad et al, ³⁶ 2011	International, multicenter, double- blind, randomized, prospective trial 0.55, 2.5, or 10 mg/kg every 4 wk for 3 doses (week 0, 4, 8)	12 and 24	2–17	0.55 mg/kg (n = 19) 2.5 mg/kg (n = 20) 10 mg/kg (n = 20)	No significant improvement in clinical symptoms using pediatric- specific EoE questionnaire. Of note, 11 of 59 subjects were already symptom free during screening period	5 of 57 subjects reached primary end point of peak esophageal intraepithelial eosinophil count of <5 per HPF at week 12 Significant decrease in peak and mean esophageal intraepithelial eosinophil counts at week 12 Higher baseline esophageal intraepithelial eosinophil counts associated with greater response to study drug Resolution of most eosinophil microabscesses and aggregations by week 12 Decreased blood eosinophil counts 24 h after first injection and low until week 12	51 of 59 subjects had AE, including (in order of decreasing frequency) vomiting, diarrhea, and upper abdominal pain 3 serious AE (chest pain, food impaction, esophageal injury caused by endoscopy)

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Table 2
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First Author, Year	Study Design and Dose	Follow-up EGD* (wk)	Age (y)	Patient Groups	Clinical Results	Immune Changes	Adverse Events
Otani et al, ³⁷ 2013	Post-hoc analysis of Assa'ad 2011	12 and 24	2–17	0.55 mg/kg (n = 19) 2.5 mg/kg (n = 20) 10 mg/kg (n = 20)	Esophageal mast cell numbers correlated with EoE symptom severity in subjects who had a >70% decrease in esophageal mast cell numbers after mepolizumab treatment	Intraepithelial mast cells were significantly decreased at week 12, particularly in subjects whose intraepithelial eosinophil count decreased to <15 eosinophils per HPF (defined in the study as responders) Mast cells were found in proximity to eosinophils in the esophagus, and mast cell/eosinophil couplets decreased significantly in responders IL-9-positive cells decreased by week 12 and correlated with mast cell numbers in responders	—
Reslizumab							
Spiegel et al, ³⁸ 2012	Prospective, randomized, placebo-controlled 1, 2, or 3 mg/kg at weeks 0, 4, 8, and 12	End of therapy or early withdrawal	5–18	1 mg/kg (n = 55) 2 mg/kg (n = 57) 3 mg/kg (n = 57)	No significant differences in the physician's EoE global assessment scores, patient's EoE predominant symptom	Peak esophageal eosinophil counts were reduced significantly more in treatment groups	Mild AE: headache, cough No serious AE related to study drug

				Placebo (n = 57)	assessment scores, and Children's Health Questionnaire scores between the treatment and placebo groups and the placebo group		
QAX576							
Rothenberg et al, ³⁹ 2015	Prospective, randomized, placebo controlled 6 mg/kg at weeks 0, 4, and 8 with option for responders who relapsed to receive open-label extension of 3 more monthly doses	12 and 33	18–48	Completed to week 12: QAX576 (n = 15) Placebo (n = 8)	No significant difference between change in Mayo Dysphagia Questionnaire score between QAX576 and placebo group	No significant difference in proportion of responders (subjects who had ≥75% in peak eosinophil count per HPF from baseline to week 12) between QAX576 and placebo group Mean esophageal eosinophil count decreased by 60% in Q group vs 23.3% in the P group QAX576 lead to normalization of EoE-related gene expression, including eotaxin-3, periostin, carboxypeptidase A3, and desmoglein-1 CXCL1, CXCL6, and DHR59 expression was significantly different at baseline between nonresponders and responders	Mild AE: cough, reflux

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Table 2
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First Author, Year	Study Design and Dose	Follow-up EGD* (wk)	Age (y)	Patient Groups	Clinical Results	Immune Changes	Adverse Events
OC000459							
Straumann et al, ³³ 2013	Randomized, placebo- controlled, parallel- group, single-center trial 100-mg OC000459 tablets, twice daily after meals for 8 wk	8 and 20 (or when symptoms reappeared between weeks 8 and 20 in subjects who had achieved remission)	22–69	OC000459 (n = 14) Placebo (n = 12)	Physician's global assessment of disease activity improved significantly only in the OC000459 group Patient-reported outcomes (measured by visual dysphagia questionnaire and pain questionnaire) improved significantly in both the OC000459 and placebo groups	In OC000459 treatment group: Significant decrease in mean eosinophil number measured in a total of 40 HPF from 294 biopsies taken from the proximal and distal esophagus Number of MCs and CD3+ T cells unchanged Epithelial expression of TSLP unchanged Significant increase in TGFβ1 expression by epithelial cells Reduced extracellular deposits of eosinophil peroxidase and tenascin C	1 severe AE unrelated to study drug: appendicitis
Omalizumab							
Foroughi et al, ⁴⁰ 2007	Single-center open-label trial 0.0073–0.025 mg/kg/IU/mL every 2 wk for 8 doses	16	33–60	EGID (n = 9)	Symptom scores (using EGID scoring system modified from Crohn Disease Activity Index) improved significantly by	Absolute eosinophil count decreased significantly by week 16 Tissue eosinophil counts decreased in the duodenum and gastric	No severe AE

					week 7–8 and week 15–16	antrum but trended upward in the esophagus Basophil and dendritic cell FcεRI expression and free IgE levels decreased significantly
Clayton et al, ⁴¹ 2014	Prospective, double-blind, randomized, placebo-controlled trial 0.016 IU/mL every 2–4 wk for 16 wk	16	—	OMA (n = 16) Placebo (n = 14)	No decrease in symptoms compared with placebo	No significant decrease in esophageal eosinophil counts compared with placebo Significant decrease in serum IgE levels compared with placebo
Loizou et al, ⁴² 2015	Open-label, single arm, unblinded trial 150–375 mg every 4 wk for 12 wk	16–20	12–35	n = 15	Symptom scores (using EGID scoring system modified from Crohn Disease Activity Index)	5 of 15 subjects achieved full remission (<15 eosinophils per HPF in esophagus) Numbers of esophageal eosinophil, mast cells, and IgE significantly decreased

Abbreviations: ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EGD, esophagogastroduodenoscopy; EGID, esophageal gastrointestinal disorder; HES, hypereosinophilic syndrome; HPF, high-power field; M, mepolizumab; P, placebo; TGF, transforming growth factor; TSLP, thymic stromal lymphopoietin.

bronchodilation, improve quality-of-life scores, and improve ACQ5 scores.^{45,53} Furthermore, in severe steroid-dependent eosinophilic asthmatics, mepolizumab had significant steroid-sparing effects.⁴⁴ Mepolizumab 100 mg administered subcutaneously every 4 weeks was recently FDA approved as a maintenance therapy for severe eosinophilic asthma in patients greater than or equal to 12 years of age.⁵⁴

IL-5 has been repeatedly implicated in atopic dermatitis pathogenesis, with atopic dermatitis being associated with blood⁵⁵ and skin eosinophilia,⁵⁶ and increased numbers of IL-5-producing cells in lesional skin biopsies.⁵⁷ A pathogenic IL-5-producing CCR8+ Th2 cell population has been reported to play a role in the chronic phase of eosinophilic atopic dermatitis.⁵⁸ However, mepolizumab did not show clinical efficacy in atopic dermatitis.⁴⁹ It has been hypothesized that the lack of clinical efficacy was caused by the inability to block tissue eosinophilia because tissue eosinophil counts were similar in mepolizumab-treated and placebo groups after atopy patch testing.⁵⁹

Mepolizumab has also been shown to be well tolerated, reduce blood eosinophil counts, and have steroid-sparing effects in hypereosinophilic syndrome.^{32,46,60–62} In addition, mepolizumab has shown promise as a potential steroid-sparing agent in 2 small (7 and 10 subjects), uncontrolled trials in patients with eosinophilic granulomatosis with polyangiitis, albeit at higher doses (750 mg) than the approved 100-mg dose for eosinophilic asthma.^{47,48} Mepolizumab was granted orphan drug status by the FDA for hypereosinophilic syndrome in 2004 and for eosinophilic granulomatosis with polyangiitis in 2011.⁵⁴

Clinical trials in adult eosinophilic esophagitis

Stein and colleagues, 2006 Mepolizumab was first investigated as a potential treatment of EoE by Stein and colleagues.³¹ In an open-label phase I/II safety and efficacy study, 4 adult patients with EoE were treated with mepolizumab intravenously at 10 mg/kg (maximum 750 mg) at weeks 8, 12, and 16. Peripheral blood eosinophilia and percentage of CCR3+ cells decreased, as well as mean and maximum esophageal eosinophil counts. Clinically, mepolizumab was well tolerated and patients reported an improved quality of life.

Stein and colleagues, 2008 Results from another open-label phase I/II study with mepolizumab administered intravenously at 10 mg/kg (maximum 750 mg) at weeks 8, 12, and 16, this time for patients with hypereosinophilic syndrome ($n = 18$), EoE ($n = 6$), and eosinophilic gastrointestinal disorder ($n = 1$), was published in 2008.³² This study again found that mepolizumab decreased serum eosinophil counts, CCR3+ cells, but not peripheral blood leukocyte, total lymphocyte, or lymphocyte subset counts. These investigators also reported that IL-5 and IL-5-R α levels seemed to increase on mepolizumab therapy. Subsequent investigation into this phenomenon found that in patients with EoE treated with mepolizumab 750 mg at weeks 0 and 1 and 1500 mg at weeks 5 and 9, IL-5-R α expression was not increased on eosinophils.³⁴

Straumann and colleagues, 2010 In the first randomized, double-blind, placebo-controlled trial, mepolizumab 750 mg or placebo was administered intravenously every week for 2 doses.³³ If remission (defined as <5 eosinophils per HPF) was not observed following the first 2 doses in the treatment arm, mepolizumab 1500 mg was administered intravenously every week for 4 weeks for 2 doses. Significant decreases in serum, and peak and mean esophageal eosinophil counts were seen, although the primary end point of less than 5 peak eosinophils per HPF was not reached. In esophageal tissue, extracellular eosinophil-derived neurotoxin (EDN)

deposition and EDN-positive cell numbers decreased, as did eotaxin-1, eotaxin-2, eotaxin-3, and IL-5 levels. The number of mast cells and CD3+ T cells did not change following treatment. Reductions in epithelial cell expression of transforming growth factor (TGF) β 1 and tenascin C were also observed in the mepolizumab group. Serum eotaxin, eosinophil cationic protein, and EDN levels decreased in the mepolizumab group only. IL-5-R α expression on blood eosinophils did not change.

Clinically, mepolizumab had an acceptable safety profile. Investigators evaluated clinical symptoms by measuring the proportion of days on which subjects reported dysphagia during the 7 days before a clinic visit, and by asking subjects whether they had global changes in EoE symptoms compared with baseline. Subjects treated with mepolizumab had greater improvement in the proportion of days with reported dysphagia and had slightly more improvement in global change of EoE symptoms. However, these changes were minimal and not clinically significant.

Although mepolizumab decreases aberrantly increased eosinophil counts in the esophagus, it has also been shown that mepolizumab does not affect physiologically normal numbers of eosinophils, T cells, and mast cells in the duodenum.³⁵

Clinical trials in pediatric eosinophilic esophagitis

Assa'ad et al, 2011 This international, multicenter, double-blind, randomized, stratified, parallel-group study was the first to investigate the effects of mepolizumab in pediatric EoE (2–17 years of age).³⁶ Pediatric patients resistant to previous EoE treatment were randomized to one of 3 treatment arms (no placebo arm): 0.55, 2.5, or 10 mg/kg of mepolizumab. Significant decreases in the mean and peak esophageal eosinophil count were seen with mepolizumab. Higher baseline intraesophageal eosinophil counts were predictive of histologic response.

Although mepolizumab led to histologic improvements and had an acceptable safety profile, significant improvements in clinical symptoms were not seen. Symptom assessment was performed using a pediatric EoE-specific questionnaire that assessed the presence and severity of abdominal/chest/throat pain, regurgitation, vomiting, and dysphagia.⁶³

Spergel and colleagues, 2012 Spergel and colleagues³⁸ were the first to investigate reslizumab in a large prospective, randomized, placebo-controlled trial. Children and adolescents ($n = 262$; 5–18 years of age) with greater than or equal to 24 eosinophils per HPF, a history of EoE symptoms, and failure to respond to at least 4 weeks of proton pump inhibitor therapy, were randomly assigned to treatment with reslizumab 1, 2, or 3 mg/kg, or placebo. Similar to prior studies, histologic improvement was seen with anti-IL-5 therapy, with a significant decrease in peak esophageal eosinophil counts. However, histologic improvement was not accompanied by clinical improvement as assessed by physician's EoE global assessments, patient's EoE predominant symptom assessments, and the Children's Health Questionnaire.

Summary

Because tissue eosinophilia is a hallmark of EoE, it follows that IL-5, a key cytokine for eosinophil activation and survival, likely plays a major role in EoE pathogenesis. IL-5 has been implicated in esophageal remodeling and esophageal dysmotility in mouse models of EoE.^{64,65} However, anti-IL-5 therapy did not lead to clinical improvement or complete histologic remission despite consistent decreases in esophageal eosinophil count. These results suggest that eosinophils are not the only cells driving pathophysiology and mediating clinical symptoms in these patients.

It is possible that using a validated scoring system for methodological tracking of symptoms in future clinical trials may provide more granularity regarding the true

clinical effects of mepolizumab. Furthermore, similar to the results of mepolizumab for eosinophilic asthma, mepolizumab may provide benefit in subsets of patients with EoE, and future research efforts focused on defining these subsets may be of benefit.

Anti-Interleukin-13

IL-13 has been implicated in EoE pathogenesis in murine models and human studies. Delivery of IL-13 into the trachea of mice can induce eosinophilia in the esophagus but not the stomach.^{66,67} Intraperitoneal injection with anti-human IL-13 antibody abrogated the development of esophageal eosinophilia.⁶⁷ In humans, IL-13 expression is increased in the esophagus of patients with EoE, and IL-13 treatment of esophageal epithelial cells induced a previously described distinct, EoE-specific esophageal transcriptome profile.^{68,69} IL-13 has also been implicated in the dysregulation of desmosomal cadherin desmoglein-1, which leads to impaired esophageal epithelial barrier function.⁷⁰

Clinical trial

Rothenberg and colleagues, 2015 The first study investigating an anti-IL-13 antibody, QAX576, as a potential treatment of adult EoE was published in 2015.³⁹ Patients (18–50 years of age; $n = 25$) with greater than or equal to 24 eosinophils per HPF and proton pump inhibitor-resistant esophageal eosinophilia were randomly assigned to QAX576 (6 mg/kg) or placebo every 28 days for 3 doses with 6-month follow-up.

QAX576 was well tolerated and led to a decrease in mean esophageal intraepithelial eosinophil counts. Normalization of EoE-related gene expression in eotaxin-3, periostin, carboxypeptidase A3, and desmoglein-1 was seen after treatment. Transcriptomal changes differed between responders and nonresponders to QAX576. Three genes in particular were associated with response to anti-IL-13: CXCL1, CXCL6, and DHRS9. In addition, there was a trend toward improvement in dysphagia severity as measured by the Mayo Dysphagia Questionnaire, although the change was not statistically significant.

Summary

Isolated IL-13 blockade did not lead to a significant improvement in clinical symptoms despite significantly decreasing esophageal eosinophilia. Similar to results from trials investigating anti-IL-5 therapy, this shows that abrogating eosinophils alone is insufficient for symptom resolution in EoE. Again, note that symptom score tracking varied between each anti-IL-5 trial and this anti-IL-13 trial, as described earlier.

Anti-Immunoglobulin E

Several studies suggest that mast cells play an important role in EoE pathogenesis. Mast cells can affect smooth muscle contractility in the EoE esophagus via production of TGF β 1 and phosphorylation of phospholamban.^{71,72} Carboxypeptidase A3 and trypsin, but not chymase, are increased in the esophagi of patients with EoE,⁷³ and mast cells have been identified as a possible diagnostic marker differentiating EoE from gastroesophageal reflux.^{74,75} Mast cells were also implicated in EoE pathogenesis in a post-hoc analysis of patients with EoE treated with mepolizumab. This analysis showed that esophageal intraepithelial mast cell numbers were significantly decreased 12 weeks after mepolizumab treatment, and that esophageal mast cell numbers correlated with EoE symptom severity in patients who had a greater than 70% decrease in esophageal mast cell numbers after mepolizumab treatment.³⁷ Blocking the binding of IgE to its high-affinity receptor, Fc ϵ RI, can inhibit IgE-mediated activation of mast cells.

Clinical trials

Foroughi and colleagues, 2007 One study has been published investigating the use of anti-IgE for eosinophilic gastrointestinal disorder (defined as presence of typical gastrointestinal symptoms, greater than or equal to 25 eosinophils per HPF in stomach or duodenum, and negative work-up for other causes of gut eosinophilia).⁴⁰ In this single-center open-label study, 9 patients were treated with omalizumab subcutaneously during week 0 and then every 2 weeks for 8 total doses. Seven of these patients had esophageal eosinophilia at baseline. It is of interest that, although omalizumab led to significant decreases in the levels of serum eosinophils and tissue eosinophils in the duodenum, gastric antrum, and gastric body, esophageal eosinophil counts trended upward. Symptom scores improved significantly after omalizumab treatment.

Clayton and colleagues, 2014 In this prospective, double-blind, randomized, placebo-controlled study, patients greater than or equal to 15 years old were randomized to omalizumab ($n = 16$) or placebo ($n = 14$) every 2 to 4 weeks for 16 weeks.⁴¹ Omalizumab did not improve symptoms or decrease esophageal eosinophil counts compared with placebo. However, this study provided interesting new data suggesting a possible role for IgG4 in EoE pathogenesis. Patients with EoE had 45-fold greater levels of IgG4 by immunohistochemistry in their esophagi and had higher serum IgG4 levels that reacted to food allergens, such as milk, wheat, egg, and nuts, compared with controls.

Loizou and colleagues, 2015 In an open-label, single arm, unblinded trial, omalizumab was administered to 15 pediatric and adult patients (aged 12–35 years) with EoE every 4 weeks for 12 weeks.⁴² Symptoms assessed by Crohn Disease Activity Index improved in 7 of the 15 subjects. Disease remission (defined as histologic improvement to <15 eosinophils per HPF and endoscopic resolution of disease) was seen in 5 patients. There were significant decreases in esophageal eosinophil and mast cell counts. Changes in mast cell numbers but not eosinophil numbers were associated with improvements in endoscopy scores.

Summary

Despite growing evidence supporting the role of mast cells in EoE, inhibiting mast cell activation and degranulation seems to be insufficient for clinical and histologic disease remission in the small numbers of patients studied. Mast cell numbers were associated with endoscopy scores, providing further evidence that mast cells are involved in EoE pathogenesis. Possibly, a combination of therapies inhibiting mast cells and eosinophils could provide sufficient benefit for symptom remission.

Prostaglandin D2 Receptor Antagonists

Prostaglandin D2 (PGD2) is rapidly produced and released by mast cells after cross-linking of FcεRI on mast cell surface. PGD2 exerts downstream inflammatory effects via the CRTH2 receptor, promoting recruitment and activation of CRTH2 receptor-expressing leukocytes such as T_H2 lymphocytes, eosinophils, and basophils.⁷⁶ OC000459 is an oral CRTH2 antagonist that holds promise as a therapeutic in T_H2-type inflammatory disorders.

Clinical trial

Straumann and colleagues, 2013 In a double-blind, placebo-controlled trial, 26 patients (aged 18–75 years) with corticosteroid-refractory or corticosteroid-dependent EoE (defined as dysphagia, ≥ 20 intraepithelial eosinophils per HPF in the esophagus, exclusion of other causes of esophageal or systemic eosinophilia) were randomized to either OC000459 100 mg or placebo tablets twice a day for 8 weeks.⁴³ OC000459

reduced esophageal eosinophil counts, and extracellular eosinophil peroxidase and tenascin C levels. The reduction in esophageal eosinophil counts, although significant, only decreased the posttreatment eosinophil load to 73.26 eosinophils per HPF. Physician's global assessment of disease activity improved significantly for patients on OC000459. However, patient-reported outcome using the visual dysphagia questionnaire was significantly improved in both OC000459 and placebo groups. Endoscopic findings were slightly but not significantly improved in the OC000459 group. Numbers of mast cells, CD3+ T cells, CRTH2 receptor-expressing CD3+ T cells and epithelial cells, and expression of thymic stromal lymphopoietin (TSLP) by epithelial cells were unchanged.

Summary

Taken together, this study suggests that OC000459 is modestly effective for EoE. However, further studies are needed to tailor the administration dose (the dose in this study was based on asthma studies and not dose-ranging studies in EoE) and identify subsets of patients with EoE subtypes for whom therapy with OC000459 would be more effective.

Potential Biologic Therapies for Eosinophilic Esophagitis

Interleukin-4 receptor antagonists (interleukin-4/interleukin-13 blockade)

IL-4 and IL-13 mediate downstream effects via a common heterodimeric receptor, IL-4R α and IL-13R α 1. It has been proposed that therapies targeting IL-4 and IL-13 separately may be ineffective because IL-4 and IL-13 have overlapping downstream effects.⁷⁷ Efforts have been directed toward targeting IL-4R α to block both IL-4 and IL-13.

Dupilumab, an mAb against IL-4R α , is arguably the most promising IL-4/IL-13 targeted therapy to date. Dupilumab not only reduced asthma exacerbations in persistent, moderate to severe asthmatics but also improved FEV₁, morning PEF, asthma symptoms score, ACQ5 score, and number of short-acting beta-agonist inhalations per day. In addition, levels of biomarkers associated with Th2 inflammation (FeNO, TARC, eotaxin-3, and IgE) all decreased in patients on dupilumab therapy.⁷⁸

Four clinical trials published together in 1 article showed the efficacy of dupilumab in atopic dermatitis. Patients with moderate to severe atopic dermatitis received dupilumab monotherapy (75 mg, 150 mg, or 300 mg every week) for 4 weeks, dupilumab monotherapy (300 mg every week) for 12 weeks, or dupilumab (300 mg every weeks) in combination with topical glucocorticoids for 4 weeks. All had symptomatic improvement as assessed by EASI-50 (Eczema Area and Severity Index), pruritus score, and investigator's global assessment score. Dupilumab also led to reduction in Th2 biomarker levels (TARC and serum IgE).⁷⁹

Analysis of skin biopsy specimens from subjects who received 4 weeks of dupilumab as part of these clinical trials showed that genes upregulated/downregulated in atopic dermatitis lesions normalized after dupilumab treatment. Notably, Th2 chemokines were suppressed. Normalization of gene transcription paralleled improvements in clinical scores.⁸⁰

Targeting the IL-4 receptor to completely abrogate downstream signaling of IL-13 may prove to be more effective than isolated IL-13 blockade in EoE.

Anti-thymic stromal lymphopoietin

TSLP is a cytokine expressed by epithelial cells that drives allergic inflammation via activation of dendritic cells,^{81,82} mast cells,⁸³ and CD34+ progenitor cells.⁸⁴ Studies suggest that TSLP acts both upstream and downstream of IL-13 to mediate allergic inflammation.^{85–87} TSLP levels are increased in IL-13-induced murine allergic

inflammation and anti-TSLP inhibits IL-13-induced allergic inflammation in mouse models.⁸⁷ TSLP can also induce murine airway inflammation that is reduced in the absence of IL-4 and IL-13.^{85,86}

There is evidence that TSLP is involved in EoE pathogenesis. In mice, epithelial TSLP overexpression can induce an EoE-like phenotype via a basophil-dependent and IgE-independent pathway.⁸⁸ TSLP expression is upregulated in the esophagi of patients with EoE,⁸⁹ and single nucleotide polymorphisms in the TSLP gene have been associated with EoE.⁹⁰ It has also been shown that TSLP expression can be induced in esophageal epithelial cells.^{90,91} As such, anti-TSLP antibodies could be trialed as a stand-alone therapy or used in combination with other biologics for synergistic effect.

Anti-interleukin-9

Th2 and mast cells are cellular sources of IL-9. IL-9 promotes mast cell expansion; mast cell expression of TGF β , IL-5, and IL-13; and enhances B-cell production of IgE.⁹² IL-9 contributes to airway mucus production by acting directly and indirectly via IL-13 on airway epithelium.⁹³ Furthermore, IL-9 is involved in TSLP-mediated allergic inflammation in the lung.⁹⁴ IL-9 production by mucosal mast cells was found to be essential for the development of food allergy in murine models.⁹⁵

In murine models of asthma, blocking IL-9 using anti-IL-9 antibody has been shown to attenuate allergic airway inflammation.⁹⁶ Anti-IL-9 antibody also reduces eosinophil numbers and IL-4/IL-4/IL-13 levels in bronchoalveolar lavage fluid as well as peribronchial inflammation following OVA challenge.^{96,97}

IL-9 may also play a role in EoE pathogenesis. Expression of IL-9 is increased in the EoE esophagus.⁶⁸ IL-9 has been implicated in interactions between mast cells and eosinophils in the esophagi of pediatric patients with EoE, and eosinophils have been proposed as one of the cellular sources (but not the only one) of IL-9 in the esophagi of patients with EoE.³⁷ Other potential sources of IL-9 include Th9 and group 2 innate lymphocyte (ILC2) cells. ILC2 cell numbers are increased in biopsy tissue of patients with active EoE compared with inactive EoE.⁹⁸ Similar to anti-TSLP, anti-IL9 antibodies could also be trialed as a stand-alone therapy or used in combination with other biologics for synergistic effect.

SUMMARY

Investigation of biologic therapies in IgE-mediated food allergy and EoE has provided insights into the pathophysiology and treatment of these chronic, allergen-mediated disorders. Much remains to be elucidated. In IgE-mediated food allergy, the use of omalizumab seems to increase tolerability of food allergen and increase safety of desensitization protocols. The results of larger studies evaluating omalizumab with OIT for peanut allergy are anticipated. In EoE, the use of biologics targeting IL-5, IL-13, IgE, and the CRTH2 receptor have had mixed results. Decreases in esophageal eosinophilia are not paralleled by symptomatic remission. Future areas of research include identification of EoE phenotypes that are responsive to biologics and investigating the use of biologics in combination with other therapies.

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