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REVIEW



Biologics in food allergy: up-to-date

Stefano Passanisi , Lucia Caminiti, Giuseppina Zirilli, Fortunato Lombardo, Giuseppe Crisafulli, Tommaso Aversa and Giovanni B Pajno 

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ABSTRACT

Introduction: In recent years, the advent of immunotherapy has remarkably improved the management of IgE-mediated food allergy. However, some barriers still exist. Therefore, the effort of researchers aims to investigate new perspectives in the field of non-allergen specific therapy, also based on the current knowledge of the pathogenesis of this disease.

Areas covered: This review aims to focus on the role of biologics as a treatment option in patients with IgE-mediated food allergy. These agents are characterized by their ability to inactivate the Th2 pro-inflammatory pathways. Biologics can be used both alone and in association with immunotherapy. Monoclonal antibodies targeting IgE, the IL-4/IL-13 axis, IL-5, and alarmins have been proposed and investigated for treating food allergy.

Expert opinion: The clinical efficacy and safety of biologics have been demonstrated in several preclinical studies and randomized controlled trials. Future studies are still required to address current unmet needs, including the identification of the optimal dose to be used by ensuring the effectiveness of therapy.

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1. Introduction – the current state

During the last years, the advent of allergen immunotherapy (AIT) has radically changed the therapeutic approach to immunoglobulin E (IgE)-mediated food allergy. In the past decades, the management of food allergy was only generic and based on the avoidance of the culprit food and the use of epinephrine in the event of severe reactions due to accidental exposure to the allergenic food. However, these passive strategies were characterized by numerous weaknesses. The avoidance diet was quite frustrating in patients, particularly in those with multiple food allergies, and it was also associated with the risk of accidental ingestion of the triggering food(s) [1]. On the other hand, epinephrine has been demonstrated to be underused during anaphylaxis due to several causes, such as the fear of needles and side effects of the drug, or poor adherence to treatment [2,3]. Food allergy immunotherapy (FA-AIT) is currently recommended by the European Academy of Allergy and Clinical Immunology as a treatment option to allow increasing the threshold of reaction in patients with persistent cow's milk, egg, or peanut allergy [4]. The most frequent route of administration of FA-AIT is the oral route. Oral immunotherapy (OIT) is based on the consumption of the allergen food in incrementally increasing doses over a specified time interval [5]. Other routes of administration of FA-AIT include sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and subcutaneous immunotherapy (SCIT). SLIT is characterized by sublingual delivery of a daily dose of

food allergen in a liquid form. The SLIT dosage is usually lower than the OIT dosage and is limited to the concentration of available extracts, which thus reduces the risk of adverse reactions but at the expense of reduced efficacy [5]. EPIT is an approach that involves the application of an allergen-containing patch to the skin to allow the absorption of the food protein by dendritic cells in the dermis. Finally, SCIT is related to subcutaneous allergen administration in incrementally increasing doses [6]. FA-AIT is an active treatment that leads to the achievement of a desensitization rate that increases the amount of food that the patient can intake without reactions and reduces the risk of potentially life-threatening events after accidental ingestion [7]. Despite these benefits, FA-AIT still has some barriers. The desensitization dose is often lower than the target dose, thereby not allowing patients to consume the normal amount of the allergenic food(s) [8]. Post-desensitization effectiveness is another unmet need of FA-AIT and, so far, the opportunity to keep daily ingestion of the triggering food to maintain the beneficial effects of desensitization is still debated because of the burden for patients and their families [9]. In some desensitization treatment programs, patients are instructed to add the allergenic food to their diet ad libitum after reaching the target dose goal. However, this approach often fails due to fear of adverse reactions.

Therefore, the effort of the researchers aims to investigate new perspectives in the field of non-allergen specific therapy for the treatment of food allergy.

2. Inside the pathogenetic mechanisms of food allergy

The approach to new therapeutic alternatives for food allergy is linked to recent advances in the knowledge of the pathogenesis of this disease. The immunological mechanism of IgE-mediated food allergy is the type I hypersensitivity that causes an abnormal response to dietary antigens, mainly proteins. The sensitization phase is represented by the first exposure to the allergen that induces an initial immune response with tolerance rupture and specific IgE production. Sensitization mainly occurs through oral food exposure, but other routes could also be involved, such as skin barrier dysfunction, especially in cases of eczema and atopic dermatitis [10,11]. Increased intestinal permeability is strongly associated with the sensitization phase. The bi-directional interplay between intestinal epithelial cells and the microbiota is an interesting aspect to consider in the development of sensitization and tolerance to food antigens [12]. The interaction of some food allergen sources with lipids is another mechanism that may allow the penetration of dietary antigens through the intestinal barrier. Food allergens can bind to lipid ligands via different structural features: hydrophobic pockets, hydrophobic cavities, or specialized domains [13]. Vitamin D deficiency, changes in pH due to antacid drugs are other factors that may interfere with intestinal permeability. Finally, some allergen fragments are small and immunogenic enough to penetrate even the intact epithelial barrier. The second contact with the allergen leads to the elicitation of allergic reactions and the appearance of clinical manifestations [14]. Once the potential food allergen has passed through intestinal epithelia and avoided the normal transport processes, a crucial role in the immune response toward such allergens is played by a group of pro-inflammatory cytokines, named alarmins. This group includes interleukin-25 (IL-25), IL-33, and thymic stromal lymphopoietin (TSLP). IL-25 stimulates type 2 innate lymphoid cells (ILC2s) to release both IL-13 and IL-5 and, together with TSLP, induces the production of IL-9, which is a mast cell growth factor correlated with intestinal mastocytosis and food-induced anaphylaxis [15,16]. In the gut, in inflammatory conditions, TSLP stimulates dendritic cells to upregulate co-stimulatory molecules like OX40L, CD80, and CD86 [17]. In addition to the effects of TSLP on Th2 cell polarization through antigen-presenting cells, TSLP can directly act on T cells, including CD4 + T cells, CD8 + T cells, and regulatory T cells [18]. IL-33 is a pleiotropic cytokine that plays a key role in the pathogenesis of several diseases, acting both as an alarmin in response to signals of tissue damage, and as an inducer of Th2 immune responses by stimulating ILC2s to release IL-5 and IL-13 [19]. IL-5, IL-9, and IL-13 induce the suppression of regulatory T cells in favor of Th2 differentiation, and the activation of mast cells [20,21]. Th2 cells produce IL-4 that promotes B cell class-switching and synthesis of antigen-specific IgE (sIgE), which bind to the surface of effector cells such as mast cells and basophils through the high-affinity IgE receptor FcεR1 leading to sensitization. Subsequent exposure to allergens causes cross-linking of the sIgE bound to the FcεR1 receptor on sensitized mast cells and basophils, leading to the release of preformed and de novo synthesized pro-inflammatory

mediators (e.g. histamine, heparin, and proteases, as well as prostaglandins, leukotrienes, and other inflammatory cytokines) [22–24]. Furthermore, IL-4 drives intestinal mast cell expansion and activation, IL-5 promotes eosinophil accumulation, and IL-13 prompts CD103+ dendritic cells homing to the draining lymph nodes wherein the dendritic cells promotes the differentiation of naïve CD4 + T cells into Th2 [25–27]. The sum effects of alarmins are an increased production of IL-4, IL-5, and IL-13 causing a downstream shift away from a tolerogenic Th1-dominant state to a pro-allergic Th2-characterized response.

Based on the understanding of these immunological mechanisms, the development of novel therapeutic approaches aims to inhibit and suppress inducer and effector cells involved in the pathogenesis of food allergy (Figure 1).

3. Biologics in food allergy

In the last decade, several studies have been conducted to evaluate the use of biologics as both monotherapy and adjunctive therapy in AIT. These agents are characterized by their ability to inactivate the pro-inflammatory pathways specific to food allergies. Biologics, if used alone, may minimize the risk of allergic reactions in the event of accidental allergen ingestion. On the other hand, their use in association with AIT may provide a safer environment in which increasing doses of allergen(s) can be introduced with a lower risk of side effects [28].

3.1. Anti-IgE treatment

Anti-IgE monoclonal antibody was the first biologic to be proposed for treating food allergy. In 2003, Leung et al. conducted a double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut to evaluate the effectiveness of Talizumab (TNX-901), a humanized IgG1 monoclonal antibody against IgE. This study revealed that TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg) [29]. After a few years, studies began to be conducted to investigate the effects of another anti-IgE (i.e. Omalizumab) on patients with food allergies. Omalizumab is a recombinant humanized monoclonal antibody that binds to the CHε3 region of IgE, thereby preventing IgE from binding to FcεR1 and FcεR2 receptors on the surface of mast cells and basophils. Omalizumab also prevents IgE from binding to FcεR1 on dendritic cells causing a reduction of the circulating free IgE levels [30,31]. The reduced expression of FcεR1 on dendritic cells has been hypothesized to enhance inhibitory effects on the allergen cascade by causing a decreased release of inflammatory mediators, including histamine and Th2 cytokines [32]. Omalizumab is currently approved for the management of adolescents and adults with allergic diseases such as moderate to severe asthma and chronic spontaneous urticaria refractory to antihistamines [33–36]. In patients suffering from these diseases, Omalizumab reduces oral-corticosteroid use. Omalizumab is also indicated as an add-on maintenance

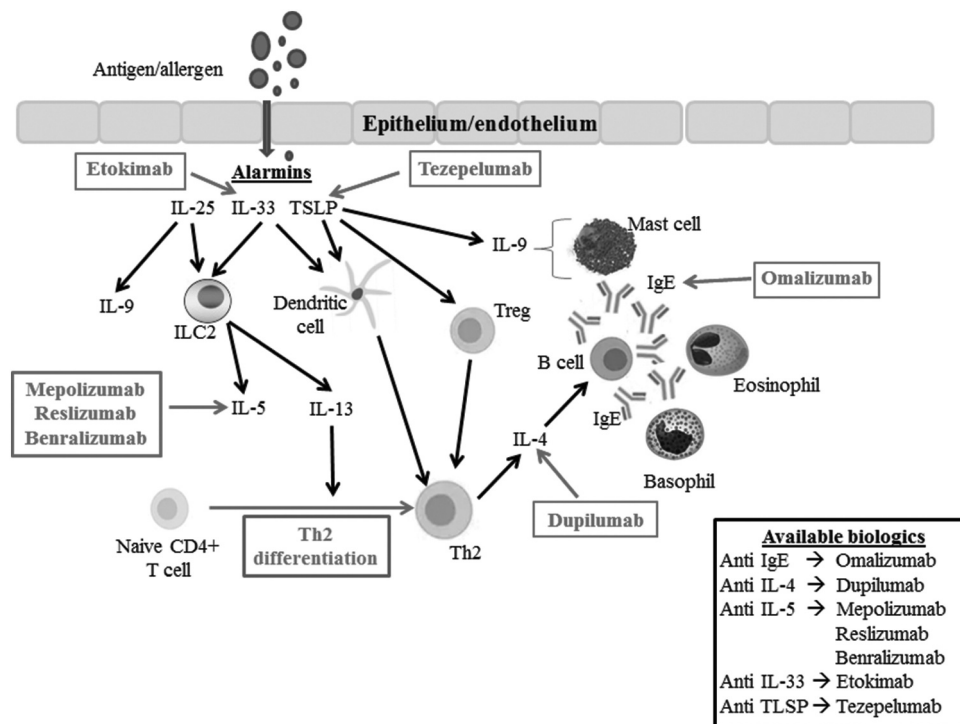


Figure 1. Main inducer and effector cells involved in the pathogenesis of food allergy against which biologics available for the management of the disease are targeted.

treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids. In 2011, Nadeau et al. conducted the first phase I study on 11 children with cow's milk allergy treated with Omalizumab in combination with rapid oral milk desensitization. Omalizumab was applied at the dose of 150 to 300 mg for 9 weeks before starting rapid oral desensitization. The build-up phase consisted of weekly up-dosing over the next 7–11 weeks while continuing Omalizumab until the 16th week to reach a maximum dose of 2000 mg of milk. Nine patients tolerated the maximum dose. After discontinuation of Omalizumab, desensitization was maintained in all these patients upon continuous administration of milk [37]. Several clinical trials on the use of Omalizumab in association with OIT have been since conducted for peanut, egg, milk, and simultaneously for multiple allergens [37–46]. All these studies reported that Omalizumab is safe and effective to achieve rapid desensitization with high rates of reaching maintenance (Table 1). Omalizumab-enabled immunotherapy mechanism of action involves four stages: pharmacological desensitization, physiological desensitization, maintenance, and sustained remission. During pre-treatment, Omalizumab avoids IgE from binding to mast cells and basophils. In this first phase, nonspecific depletion of surface-bound IgE results in decreased reactivity to allergens (pharmacological desensitization). Food allergen introduced during OIT binds to IgE, thereby triggering endocytosis. After digestion of IgE-allergen immune complexes, the IgE receptor is recycled to the mast cell surface and it is available to bind new food allergen. Then, regular exposure leads to a systematically degradation of newly food-specific IgE (physiological desensitization). At the end of Omalizumab treatment, mast cells slowly rearm with IgE. In this phase, patients remain

desensitized as long as they are ingested regularly (maintenance). After 3–5 years, the depletion of the allergic immune response may allow some patients to discontinue food allergen doses with a very low risk of losing protection (sustained remission) [47]. In most clinical trials, the first dose of Omalizumab was given at least 4 weeks before patients began immunotherapy, and treatment with anti-IgE was discontinued after 20–24 weeks when a satisfactory maintenance dose was reached. Although all studies showed a low rate of adverse events, especially in terms of severe reactions, some patients experienced mild to moderate symptoms that most commonly affected the gastrointestinal system. Regarding the feasibility of long-term sustained desensitization, recent studies have been published. Andorf et al. conducted a 5-year follow-up observational study on 34 patients with food allergy. After reaching the maintenance dose of 2 g protein for each of their respective food allergens, the long-term maintenance dose was reduced for some participants. At the end of the long-term follow-up, each patient passed the 2 g oral food challenge demonstrating the persistence of the desensitized status [48]. Similar findings were found in another observational study [49]. A randomized controlled study on multi-food allergic subjects showed that sustained desensitization after Omalizumab-facilitated multi-OIT occurs through continued maintenance OIT dosing of either 300 mg or 1 g of each food allergen as opposed to discontinuation of multi-OIT [50]. However, the recurrence of symptoms within few months from the discontinuation of Omalizumab in some patients has also been reported [51]. The dose-related efficacy of Omalizumab-enabled immunotherapy remains another of the unresolved issues. Considering the high cost of medication, the identification of the optimal dose to be used is quite

Table 1. Summary of clinical studies concerning omalizumab-enabled immunotherapy for the treatment of food allergy.

Ref	Year	Study design	Population characteristics	Outcomes
37	2011	Open label phase I study	11 patients (aged 7–17 ys) with cow's milk allergy	<i>Efficacy:</i> 81.8% patients reached a dose of 2000 mg/d within a period of 7 to 11 weeks and passed OFC to 3000 mg (8 weeks after stopping Omalizumab) <i>Safety:</i> mean frequency for total reactions was 1.6% (71% mild, 19% moderate, 10% severe)
38	2011	Randomized double-blind placebo-controlled study	14 patients with peanut allerg. Participants were randomized to receive Omalizumab ($n = 9$, mean age 16.3 ys) or placebo ($n = 5$, mean age 22.5 ys)	<i>Efficacy:</i> 4 (44.4%) omalizumab-treated subjects versus 1 (20%) placebo-treated subject tolerate >1000 mg peanut flour during an OFC after 24 weeks of treatment. <i>Safety:</i> mild to moderate adverse events were reported in both groups (placebo 88.9%, and omalizumab 76.5%) and two mild adverse events were reported to omalizumab and none to placebo.
39	2013	Open-label pilot study	13 patients (aged 8–15 ys) with peanut allergy	<i>Efficacy:</i> 92.3% patients reached the dose of 4000 mg peanut flour/day in a median time of 8 weeks and subsequently tolerated a challenge with 8000 mg peanut flour (10–12 weeks after stopping Omalizumab) <i>Safety:</i> reported reactions were 2% of total doses (87.5% were mild)
40	2014	Open-label phase 1 study	25 patients (aged 4–15 ys) with multiple food allergy	<i>Efficacy:</i> 76% patients tolerated up to 1250 mg of each food the initial escalation day. All participants reached their maintenance dose of 4000 mg protein per allergen at a median of 18 weeks. <i>Safety:</i> 5.3% of reactions for total doses (94% were mild)
41	2016	Open-label pilot study	5 patients (aged 3–11 ys) with cow's milk allergy and 9 patients (aged 5–13 ys) with egg allergy	<i>Efficacy:</i> all patients reached the maximum dose maintenance with daily 6600 mg protein of cow's milk and 1800 mg protein of egg white within 18 weeks. All the egg-allergic patients passed the challenge with 3500 g protein of row egg white after completing the induction phase. <i>Safety:</i> only four patients (28%) developed mild allergic reactions
42	2016	Randomized double-blind placebo-controlled study	55 patients (aged 7–32 ys) with cow's milk allergy. Participants were randomized 1:1 to receive Omalizumab ($n = 28$) or placebo ($n = 27$)	<i>Efficacy:</i> no differences were found in desensitization and sustained unresponsiveness between groups. Omalizumab group required less time to achieve maintenance. <i>Safety:</i> adverse reactions were markedly reduced during OIT escalation in Omalizumab subjects for percent doses/subject provoking symptoms, dose-related reactions requiring treatment, and doses required to achieve maintenance.
43	2017	Randomized controlled study	16 patients (aged 6–14 ys) with cow's milk allergy. Participants were randomized to receive Omalizumab ($n = 10$) or not ($n = 6$)	<i>Efficacy:</i> all patients in the Omalizumab group tolerated 200 mL of fresh cow's milk for a median of 17 days. Significant differences were found between group in desensitization assessed by double-blind controlled placebo food challenge and open food challenge performed after 8 weeks from stopping Omalizumab. <i>Safety:</i> a total of 0.012 and 0.028 adverse reactions per dose per child occurred in the escalation phase and in the maintenance phase, respectively. None of these reactions require epinephrine.
44	2017	Open-label phase 2 study	23 patients (aged 12–19 ys) with peanut allergy	<i>Efficacy:</i> after 8–32 weeks with Omalizumab, all patients tolerated at least 840 mg of peanut protein, and 65% patients completed the 2800 mg peanut protein final dose. <i>Safety:</i> Severity of reactions was significantly lower at the second challenge compared to inclusion challenge.
45	2017	Randomized, double-blind, placebo-controlled study	37 patients (aged 6–19 ys) with peanut allergy. Participants were randomized to receive Omalizumab ($n = 29$) or placebo ($n = 8$).	<i>Efficacy:</i> 79% of Omalizumab group tolerated 2000 mg of peanut 6 weeks after stopping Omalizumab compared to 12.5% of placebo group; 76% of Omalizumab group tolerated 4000 mg peanut 12 weeks after stopping Omalizumab, compared to 12.5% in placebo group. <i>Safety:</i> overall reaction rates were not significantly lower in Omalizumab- versus placebo-treated subjects, although Omalizumab-treated subjects were exposed to much higher doses of peanut.
46	2018	Randomized, double-blind, placebo-controlled study	48 patients (aged 4–15 ys) with multiple food allergy. Participants were randomized 3:1 to receive Omalizumab ($n = 36$) or placebo ($n = 12$)	<i>Efficacy:</i> after 20 weeks from the last Omalizumab administration, a significantly greater proportion of the Omalizumab (83%) vs. placebo (33%) participants passed double-blind controlled placebo food challenges to 2 g protein for ≥ 2 of their offending foods. The same individuals also tolerated 4 g protein of ≥ 2 foods. A greater proportion of Omalizumab (77%) vs. placebo (0%) participants passed a DBPCFC to 2 g protein for ≥ 4 of their offending foods. <i>Safety:</i> No serious or severe adverse events were reported.

relevant. A recent study conducted with the primary endpoint to identify determinants of Omalizumab dose-related efficacy in oral immunotherapy showed that Omalizumab dosages should be adjusted for bodyweight alone, independently of total IgE. Furthermore, the fraction of allergen-specific/total IgE could be useful to predict patients at greater risk of food dosing reactions upon weaning [52]. Another phase 2b clinical trial that compares two dosages of Omalizumab (8 mg/kg per month and 16 mg/kg per month) to placebo during a symptom-driven multi-OIT protocol is ongoing [47].

Interestingly, omalizumab treatment affects both total and allergen-specific IgE levels. Mizuma et al. were the first to observe a negative to positive seroconversion rate for some allergens in patients treated with Omalizumab [53]. Although the underlying mechanism leading to IgE elevation remains unsolved, this effect has important clinical relevance as the IgE-diagnostic may be influenced by Omalizumab treatment. Therefore, it may be useful to collect and store more patient serum before anti-IgE therapy for potential future diagnostic procedures.

Few studies concern the use of Omalizumab as monotherapy for food allergy. Dahdah et al. reported their experience on Omalizumab used to treat a boy with severe asthma and anaphylaxis to multiple foods after preparatory selective IgE apheresis. The patient became partially or fully tolerant to the offending foods within 40 days after the start of Omalizumab, with an improvement in his quality of life [54]. A report from Sweden described the effectiveness of Omalizumab for the treatment of children with severe milk allergy including episodes of anaphylaxis. The authors demonstrated the usefulness of basophil allergen threshold sensitivity (CD-sens) to avoid risky food challenges [55]. CD-sens has been also demonstrated to be used to individualize the dosage of Omalizumab for the management of severe peanut allergy [44].

Another anti-IgE therapeutic option is Ligelizumab, which is a humanized, recombinant, monoclonal IgG1K antibody. Comparing in vitro data to Omalizumab, Ligelizumab has been demonstrated to have an almost 50-fold higher affinity for human IgE and to be more effective at blocking IgE-dependent mast cell degranulation [56]. Basophil activation testing and the enzyme-linked immunosorbent facilitated antigen-binding assays revealed that Ligelizumab inhibits IgE binding to effector cells without displacing receptor-bound IgE [57]. To date, Ligelizumab has been tested solely for the management of chronic spontaneous urticaria. Researches on the potential use in patients with food allergy are awaited.

3.2. Anti-IL-4 and IL-13 treatment

As previously described, IL-4 and IL-13 promote Th2 cell differentiation, which mediates the pro-allergic adaptive immune response [20,21]. IL-4 has two types of receptors: the type 1 receptor, which is composed of the IL-4 chain (IL-4R α) and a γ chain (γ C), and the type 2 receptor, which is composed of the IL-4R α chain and the α 1 chain of the IL-13 receptor (IL-13R α 1) [58]. The type 1 receptor can be activated by IL-4, while the type 2 receptor can be activated by both IL-4 and IL-13. Ligand

binding to these receptors activates a signal transduction cascade that mainly leads to the modulation of expression of genes involved in IgE class switching and Th2 cell differentiation [59,60]. Among several biologics targeting the IL-4/IL-13 axis, Dupilumab has emerged as one of the most successful therapies. Dupilumab is an IgG4 human monoclonal antibody that binds IL-4 receptor alpha subunit (IL-4R α). The precise mechanism of action of this biologics is not yet clear. It has been hypothesized that Dupilumab may simultaneously inhibit IL-4 binding to IL-4R α and inhibit the recruitment of γ C to the IL-4R α chain. Besides, it may also suppress the recruitment of IL-4R α to IL-13R α 1 [61]. Dupilumab is currently approved by both the Food and Drug Administration (FDA) and the European Medicines Agency for the management of moderate-to-severe atopic dermatitis [62,63]. In 2018, the FDA has also approved Dupilumab for treating asthma and, more recently, as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis [64]. Abdel-Gadir et al. found that treatment with anti-IL-4R α monoclonal antibody in peanut-allergic patients augmented the suppressive function of peanut-reactive regulatory T cells, highlighting the potential disease-modifying effect of anti-IL4 therapy [65]. The first clinical experience on Dupilumab in the treatment of food allergy was described by Rial et al. who reported the case of a 30-year-old woman with severe atopic dermatitis and allergy to corn and nuts. The patient was treated with Dupilumab at an initial dose of 600 mg, followed by 300 mg every 2 weeks. After 3 months of treatment, she became desensitized and passed a confirmatory oral food challenge to corn and nuts [66]. Currently, there are two ongoing studies to evaluate the safety and efficacy of Dupilumab in food allergy, used both as adjunctive therapy to OIT and as a monotherapy in peanut allergy [67,68]. Another phase 2 randomized clinical trial to evaluate the effectiveness of Dupilumab-enabled immunotherapy in patients with a history of multiple food allergies including peanut is also under investigation [69].

3.3. Anti-IL-5 treatment

IL-5 is another cytokine that exerts a central pathogenetic role in mediating Th2 response. It is synthesized and secreted by various cells, such as eosinophils, Th2 cells, mast cells, natural killer T cells, and ILC2s [70]. IL-5 is the most important biological factor responsible for differentiation, recruitment, survival, and degranulation of eosinophils [71,72]. The biological effects of IL-5 are mediated by its selective interaction with the IL-5 receptor (IL-5 R), which is composed of a specific α subunit (IL-5 R α) and a nonspecific β C heterodimer, which can be recognized also by IL-3 and granulocyte macrophage colony stimulating factor [73]. IL-5 binds as a homodimeric protein to IL-5R α , which is highly expressed on the eosinophil surface, thus recruiting the β C dimer and inducing the assembly of the IL-5/IL-5R α / β C ternary complex [70,74]. Currently, there are three biologics, namely Mepolizumab, Reslizumab, and Benralizumab, targeting the pathogenic IL-5/IL-5R pro-eosinophilic axis. Mepolizumab and Reslizumab are both humanized monoclonal antibodies that bind to IL-5, preventing its interaction with its receptor, whereas Benralizumab is a

monoclonal antibody that acts as an IL-5 receptor antagonist by binding to the α -chain of IL-5 receptor on eosinophils and basophils [10]. These biologics have a steroid-sparing effect in eosinophil disorders, such as eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, eosinophilic esophagitis, and chronic eosinophilic pneumonia [75–77]. The benefits of using anti-IL-5 agents in eosinophilic gastrointestinal disorders are promising prerequisites for their potential application in the management of food allergies as well. In fact, eosinophilic gastrointestinal disorders, mainly eosinophilic esophagitis, have been proposed as a variety of chronic food allergies that share several genetic and environmental linkages with IgE-mediated FA. Some authors suggested that eosinophilic gastrointestinal disorders and IgE-mediated FA could be considered two forms of food allergy that may be in dynamic equilibrium with each other, presenting challenges but also opportunities in management [78].

3.4. Anti-alarmins treatment

As discussed above, alarmins are critical for inducing and maintaining food allergy as they play a crucial role in determining the Th2 response. Khoudoun et al. evaluated the potential role of monoclonal antibodies neutralizing TSLP, IL-25, and IL-33 to prevent food allergy development in a mouse model. Those authors found that combined treatment with antagonists to all three alarmins strongly inhibited food allergy development, but no single monoclonal antibody could suppress established food allergy [79]. Some studies revealed that antibodies toward IL-33 could be promising as treatments of allergic diseases, such as asthma and atopic dermatitis [80–83]. In a murine model of allergic rhinitis sensitized to ovalbumin, anti-IL-33 treatment was effective in improving allergic symptoms and reducing both total and allergen-specific IgE in the serum [84]. IL-33 is released from the epithelial cells and different tissue and organs. This interleukin exerts its action on the surface of mast cells and T cells, by the receptor T1/ST2 [85]. This receptor is also involved in the secretion of pro-inflammatory factors, such as leukotrienes, IL-6, and TNF- α [86]. Etokimab, a humanized immunoglobulin subtype G1/k monoclonal antibody, is the most investigated biologic as a specific antagonist to IL-33. A phase 1 trial of Etokimab in healthy volunteers indicated a favorable safety profile and pharmacodynamic properties [87]. A phase 2a randomized, placebo-controlled study was conducted to evaluate the safety and the ability of a single dose of Etokimab to desensitize peanut-allergic adults. Participants who received either etokimab ($n = 15$) or placebo ($n = 5$) were tested with oral food challenges at days 15 and 45. Results indicated a significant increase in desensitization to peanut protein after a single intravenous administration of Etokimab for the active group. The Etokimab group had fewer adverse events compared with the placebo [88].

Similar to IL-33, an anti-TSLP antibody has also been developed for human use. TSLP exerts its effects by binding to a high-affinity heteromeric receptor complex composed of the TSLPR chain and IL-7R α [89]. Tezepelumab is a human monoclonal antibody that binds to TSLP and inhibits its interaction

with the TSLP receptor complex [90]. While some studies investigating the use of Tezepelumab reported encouraging results as it seems to reduce asthma exacerbations in patients with moderate-to-severe asthma [91,92], its application for the management of food allergy has not been evaluated.

Finally, the use of biologics toward IL-25 in humans has not yet been investigated.

4. Expert opinion

In recent years, allergy specialists have been able to take a step forward in the management of IgE-mediated food allergy. Immunotherapy strategies have been developed and introduced into clinical practice. The most recent guidelines strongly recommend the use of FA-AIT as potentially curative therapy. However, this treatment option can only be practiced in selected medical centers and under strict medical supervision. In this context, the advent of biologics in association with immunotherapy represents an interesting therapeutic option to reduce the side effects of AIT and, at the same time, achieve rapid desensitization with high rates of sustained remission. Preclinical studies and clinical trials have been increasingly conducted on the use of biologics, particularly on Omalizumab, in conjunction with immunotherapy. Most of these studies reported encouraging results in terms of safety and effectiveness. However, the high cost of biological agents may represent a weakness of this emerging therapeutic approach. A crucial way to decrease costs is by rationalizing the use of expensive medication. Therefore, future researches will be focused on the identification of the optimal dose to be used by ensuring the efficacy of therapy. Regarding the role of biologics as monotherapy, although their use appears to be effective in reducing the risk of allergic reactions in the event of consumption of triggering food(s), clinical trials in this field are awaited.

One of the most promising areas for improving immunotherapy strategies is the attempt to introduce agents capable of inactivating dendritic cells. On mucosal surfaces, dendritic cells sample luminal content through the epithelium, receive and manipulate antigens provided by goblet cells, and sample the lymphoid tissues. After antigen recognition, dendritic cells migrate to lymph nodes and promote tolerance by presenting the antigen to T cells. They are mainly activated by their innate immunity receptors, the Toll-like receptors (TLRs), which could be targeted by biologic agents. TLRs represent a family of pattern recognition receptors that play a key role in the innate immune response. TLRs protect the host from pathogens, but also recognize host-derived molecular patterns as a warning signal and lead to inflammation without infection, thus contributing to the development of several inflammatory and autoimmune diseases. To date, 10 human (TLR 1–10) and 13 murine (TLR 1–9, 11–13) functional subtypes of TLR have been identified. Various therapeutic agents to suppress TLR signaling have been developed and can be classified as small molecule inhibitors, antibodies, oligonucleotides, lipid-A analogs, microRNAs, and nano-inhibitors. Among these molecules, CpG oligodeoxynucleotides have already been tested in preclinical studies with promising results. CpG

oligodeoxynucleotides suppress Th2 response by binding to TLR-9, increasing IL-12, IL-10, IL-22, and decreasing TSLP. CpG oligodeoxynucleotides have also been coupled to virus-like particles that are characterized by a viral capsid and are used as platforms for immune recognition, uptake, and processing. Efficacy trials conducted on adult patients with allergic rhinitis showed that CpG oligodeoxynucleotides associated with virus-like particles are safe and may lead to significant clinical improvements. However, none of these approaches has yet been investigated in the field of food allergy. More importantly, it is necessary to establish the long-term effects of these therapies as they may impair local immune defenses.

In our opinion, the time is ripe to meet patients' expectations for lasting relief of symptoms caused by food allergy. Current knowledge on the action of biologics regarding the blocking of Th2 pro-inflammatory pathways supports the thesis that these agents are the most promising therapeutic option to achieve this goal, as already demonstrated by the successful experience of Omalizumab and Dupilumab in the management of other allergic diseases, such as asthma and atopic dermatitis. Future studies are still required to identify which class of biologics will allow obtaining the best effectiveness along with a good safety profile, low costs, and short duration of treatment.

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