Italian Journal of Pediatric Allergy and Immunology number **04** | **2025** | 24-31

Update on Biologic Therapy in Food Allergy

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Special Issue: Update on Biologic Therapy in Pediatric Allergy

ABSTRACT

Purpose of review. The landscape of biological therapies for allergic diseases is experiencing rapid growth. Food allergy was not the first to be targeted, but the research community has recently begun to recognize the unmet needs in this area. Herein we summarize the state of the art for children experiencing food allergies, with emphasis on the potential scenarios that will open up in the near future.

Recent findings. Over the past decade, several promising strategies have emerged as alternatives to simply eliminating the offending food, which carries the risk of serious adverse reactions. Desensitization via oral immunotherapy has been integrated into clinical practice as a treatment strategy, with the recent inclusion of omalizumab. Furthermore, various delivery methods for immunotherapy, other biologics, small molecules, IGNX001, and PVX108 are being explored.

Summary. The range of accessible therapeutic options for food allergies is expanding; however, significant unmet needs persist. This review aims to provide a concise summary of current and potential therapies for IgE-mediated food allergies and their prospects.

KEY WORDS: biologicals, food allergy, immunotherapy, omalizumab, small molecules

INTRODUCTION

"A harmful response that emerges as a discrete and repetitive immunological reaction to the administration of a specific food" is what food hypersensitivity is defined as [1]. Food allergies are a serious public health hazard that is growing at an alarming rate. It is thought to affect more than 500 million individuals worldwide, frequently starting in early childhood.

Prior to the past 10 years, and even now in many countries, especially those with low per capita income, the mainstay of management was strict dietary avoidance of food triggers and the use of emergency medications to treat allergic reactions in cases of unintentional exposure. However, in recent years, there have been notable advancements in the available therapeutic choices. The first standardized product approved for peanut oral immunotherapy (OIT) in 2020 and the first evidence-based guidelines on OIT published in 2017 were especially significant [2,3]. More recently, in February 2024, the U.S. Food and Drug Administration (FDA) approved omalizumab for use in children with food allergies who were at least one year old. Nonetheless, a number of restrictions still exist, primarily with regard to long-term outlooks and the discovery of trustworthy response biomarkers. Furthermore, there has been much recent research on different ways to provide immunotherapy, other biologics, small compounds, probiotics or prebiotics, microbiota transplantation therapy, IGNX001, and PVX108. The most recent findings regarding the current range of treatment choices and the main therapies under study will be summarized in this review.

Received: October 16, 2025
Published: January 23, 2026

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How to cite this article: Fiocchi A, Fierro V, Arasi S, et al. Update on Biologic Therapy in Food Allergy. Italian Journal of Pediatric Allergy and Immunology 2025;39(04):24-31. https://doi.org/10.53151/2531-3916/2025-1752

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CLINICAL FEATURES OF FOOD ALLERGY

Childhood food allergies can involve various immunological pathways. The primary type identified is categorized as IgE-mediated food allergy (FA) [4], which is specifically addressed herein. The spectrum of clinical signs associated with FA can vary, encompassing dermatological, gastrointestinal, respiratory, circulatory, and/or neurological indicators. The intensity of allergic reactions may range from mild localized symptoms to severe systemic responses, which can potentially culminate into life-threatening anaphylaxis [5]. Effective and tailored management of FAs necessitates an accurate evaluation of the overall severity of food allergies as a comprehensive condition. In 2023, a global consensus presented the DEFASE (Definition of Food Allergy Severity) score, marking the inaugural international exhaustive classification of FA severity [6]. This scoring framework takes into account symptoms, health-related quality of life (HRQoL), and financial aspects for a patient-centric evaluation [7,8].

1. MANAGEMENT OPTIONS – CURRENTLY APPROVED

1.1 Elimination diet and emergency treatment

The traditional approach to FA places a strong emphasis on avoiding trigger foods and having emergency allergy medication on hand in case an unintentional allergic reaction happens. However, there are drawbacks to a management approach that only uses elimination diets. Reduced dietary variety, possible nutritional deficits, social constraints that may impact the HRQoL of patients and their families, and persistent anxiety resulting from the fear of severe reactions from unintentional exposure to allergens are some of the shortcomings [9].

The significance of oral food challenges (OFC) in establishing personal reaction thresholds has been emphasized by recent research. Building on this study and working with the food industry to develop guidelines for more precise labeling that reports allergen levels rather than ambiguous phrases like "may contain traces of" is the challenge that lies ahead. In the end, this would provide patients with high reactivity thresholds more choices [10].

To avoid overdiagnosis and needless usage of specific formulae, there have been notable developments in the diagnosis and treatment of cow's milk protein allergy (CMA) in recent decades. According to guidelines, breastfeeding is the best course of action for newborns and infants with allergies. Only nursing mothers of infants who have chronic symptoms are advised to follow a maternal elimination diet. The most recent guidelines advise using substantially hydrolyzed cow's milk or hydrolyzed rice-based formula as the first option if breast milk is not available, followed by formula based on amino acids and, as a last resort, soy-based formula [11].

The administration of self-injectable adrenaline is another essential component of FA therapy, in addition to the elimination diet. When anaphylactic reactions occur, prompt intramuscular epinephrine is the first-line and most effective treatment; delayed administration has been associated with increased risk of morbidity and mortality, including fatal outcomes [12].

1.2 Oral Allergen-specific Immunotherapy (OIT)

Allergen-targeted immunotherapy (AIT) has the capacity to alter the clinical expression of allergic conditions by providing small, escalating doses of the responsible allergen over a prolonged duration [13,14]. The immediate aim is to allow the individual to ingest the problematic food without triggering significant reactions [15]. The overarching goal of AIT is to attain both clinical and immunological tolerance (i.e. the absence of an allergic response to the allergen, even post-treatment cessation). The phrase "sustained unresponsiveness" refers to the ability to safely consume a standard amount of food containing the allergen in question, despite a period of halted treatment and, consequently, no ongoing exposure [16]. However, this goal requires years to achieve and is realized only by a specific group of patients [17]. Oral immunotherapy (OIT) is currently the most prevalent method and involves the methodical oral delivery of incrementally larger quantities of specific allergenic food. OIT strategies differ regarding the amount of allergen given, the pace of dose escalation, and the ultimate target dosage [13,18]. Typically, protocols consist of an initial escalation phase with increasing doses administered in a clinical environment, with patients then continuing to take the maximum tolerated dose at home. In 2018, EAACI first recommended OIT as a treatment option in a clinical context for children with persistent allergies to cow's milk, eggs, or peanuts to elevate the reaction threshold during treatment [3]. Importantly, most children with milk/egg/soy allergies naturally outgrow the food allergies. Additionally, 50-75% of children with cow's milk allergy can tolerate baked items containing dairy [19]. Consistent exposure to baked milk may herald a faster development of tolerance, and allows the reintroduction of biscuits and cookies. It may also prompt some practitioners to utilize baked milk for desensitization with variable effectiveness, by an adaptable home-based method referred to as the "ladder" [20,21] (Fig. 1) [22]. Present evidence suggests that egg OIT can desensitize ≥ 80% of treated children [23].

A study reported that following prolonged treatment with egg-OIT, between 27.5% and 50% of participants achieved sustained unresponsiveness between the second and fourth years of therapy [24]. A meta-analysis by the GA2LEN group showed that OIT efficiently prompts desensitization to peanuts, although there is limited evidence for sustained unresponsiveness [22]. Palforzia® (AR101), a standardized formulation of pharmaceutical-grade peanut-OIT, received FDA and European Medicines Agency (EMA) approval in January and December 2020, respectively. During a double-blind, placebo-controlled OFC, 58-67% of OIT participants were able to tolerate 600-1000 mg of

peanut proteins compared to 25% in the placebo group [2]. A pilot study assessed the safety and effectiveness of OIT utilizing lyophilized peanut protein-MH, a peanut-derived formulation with reduced allergenic potential due to cooking [25]. Peanut-allergic children with a maximum tolerated dose of peanut protein ≤ 100 mg were enlisted in a 40-week OIT protocol, receiving 300 mg daily of freeze-dried, heat-treated peanut protein. The mean cumulative tolerated dose (MCTD) prior to OIT initiation was 71.2 mg of peanut protein, although 32 of 33 participants managed to consume ≥ 300 mg of peanut protein after 40 weeks. Following 6-12 months of daily maintenance, the MCTD rose to 8821 mg.

Early OIT research has demonstrated more favorable outcomes concerning the establishment of sustained unresponsiveness in children under the age of 4, especially in the youngest children with lower IgE levels (Fig. 2) [26], and this was further validated in studies addressing epicutaneous immunotherapy (EPIT) [27,28]. Nonetheless, the underlying mechanisms are not completely understood.

1.3 Alternative routes of administration in advances state of evaluation: epicutaneous and sublingual immunotherapy

Epicutaneous (EPIT) and sublingual (SLIT) immunotherapy have been explored to improve the safety profile of oral immunotherapy (OIT). The likelihood of systemic reactions remains remarkably low due to the administration of minimal allergen quantities via these methods. They do not raise the reactivity threshold in the short term or to levels comparable to those achieved with OIT, but appear to elicit analogous changes in the immune response to antigens over time; preliminary data suggest that these therapies may offer long-term advantages once the treatment is stopped [27].

De Boissieu et al. carried out an open-label trial involving SLIT in 8 children suffering from cow's milk allergy (CMA). Three of these children showed desensitization to 200 mL of cow's milk [29].

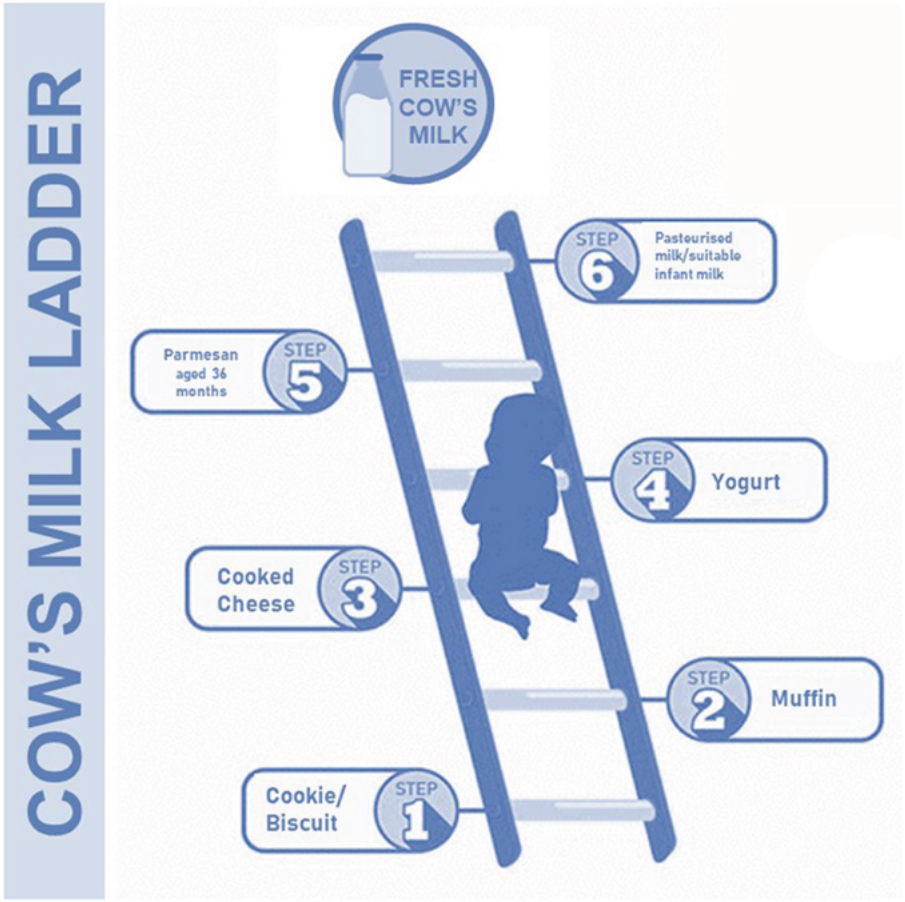


FIGURE 1. Example of cow's milk ladder (from Carucci L, Coppola S, Luzzetti A, et al. Immunonutrition for Pediatric Patients with Cow's Milk Allergy: How Early Interventions Could Impact Long-Term Outcomes. Front Allergy 2021;2:676200. https://doi.org/10.3389/falgy.2021.676200. Copyright © 2021 Carucci, Coppola, Luzzetti, Voto, Giglio, Paparo, Nocerino and Berni Canani (CC BY)) [22].

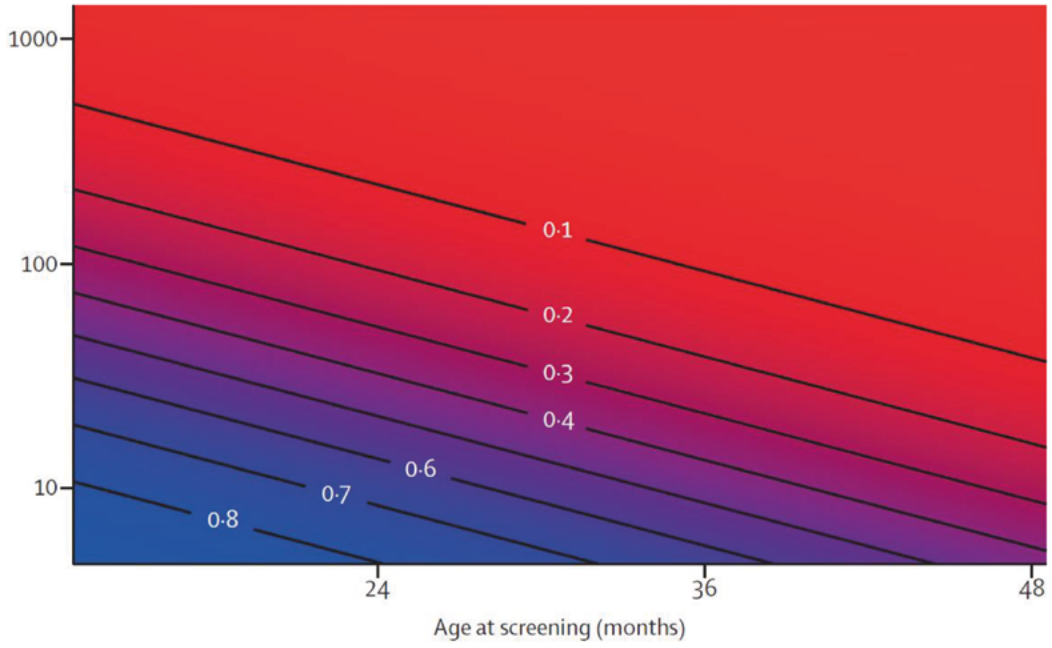


FIGURE 2. OIT: the earlier, the better? (from Jones SM, Kim EH, Nadeau KC, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet 2022;399:359-371. https://doi.org/10.1016/S0140-6736(21)02390-4) [26] (All necessary permissions for publication have been obtained).

Greenhawt et al. carried out a phase 3 trial focused on peanut-allergic children aged 1 to 3 years. The peanut patch therapy applied at 12 months enabled the intervention group to safely ingest three to four peanuts, or a single peanut equivalent, of peanut protein, depending on their sensitivity to peanuts [30]. Furthermore, a randomized clinical study revealed that a daily dose of 300 µg of Viaskin®Milk (EPIT) over 12 months led to statistically significant desensitization in children with CMA aged 2-11 years, boasting an excellent safety record [31].

1.4 Omalizumab

The foundational investigations into biological treatments for food allergies (FAs) began in 2003 with TNX 901 [32]. Subsequently, the emphasis shifted to omalizumab [33-35]. Omalizumab is a monoclonal antibody that binds to the constant region of serum IgE (Fig. 1). Multiple studies have shown encouraging outcomes in the management of FAs [36,37]. In 2024, results from the first phase of the double-blind, randomized, placebo-controlled OUTMATCH trial conducted on patients aged ≥ 1 year with multiple food allergies demonstrated the efficacy of omalizumab for desensitization as a standalone therapy and assessed its safety. Patients in the omalizumab cohort, who could ingest ≥ 600 mg of peanut protein without experiencing dose-limiting symptoms, exhibited an approximate 10-fold enhancement compared to the placebo cohort. The reactivity threshold to prevalent allergens like cashew, egg, and milk was increased, while potential reactions to accidental ingestion were effectively managed with omalizumab over a 16-week period, showing superiority over placebo [38]. In February 2024, the FDA granted approval for omalizumab as a treatment for food allergies in the United States for individuals aged one year and older to mitigate the risk of accidental reactions. However, it has not received approval for food allergies in Europe. Recently, our group in Italy published the findings of the OSAFA study, which involved patients with severe asthma and concomitant food allergies. We found that 40 of 65 patients could tolerate the amount of food permissible under omalizumab [39]. Omalizumab has also been investigated in conjunction with both single and multiple-food OIT to enhance safety and reduce the duration of the OIT build-up phase, yielding positive results overall [40,41]. Additionally, omalizumab was juxtaposed with placebo in an accelerated mOIT protocol by Andorf et al. where 83% tolerated 2 g of protein from two food sources after 7 months, compared to 33% in the placebo group [34]. The treatment failure rates were 8% and 67% in each group at 8 weeks. Azzano et al. reported that the dose-dependent effects of omalizumab on reactivity thresholds prior to OIT were affected by weight-based dosing, but not by typical asthma-related weight dosages or IgE levels. Specifically, an elevation in reactivity threshold was linked to reduced concentrations of free specific IgE, increased levels of free omalizumab, and heightened amounts of specific IgE-omalizumab complexes [42].

2. MANAGEMENT OPTIONS CURRENTLY UNDER EVALUATIONS

2.1 Biologics different from omalizumab

A stronger anti-IgE monoclonal antibody, ligelizumab, after having raised some initial hopes [43], it has now been abandoned in its development program [44]. Another biologic medication investigated for the treatment of FAs is dupilumab. Even this, after showing some promise, has not confirmed to be able to help in accompanying or replacing OIT for peanuts [45,46]. Anti-IL-33 (etokimab) has shown encouraging results in early trials for peanut allergies [47].

2.2. Small molecules

An important enzyme in IgE-mediated signaling pathways, Bruton's tyrosine kinase (BTK) is thought to be a possible therapeutic target for allergic reactions. BTK-inhibiting small molecules, such as ibrutinib and acalabrutinib [48], might work well as supplemental treatments to control the negative effects of OIT. Notably, these BTK-targeting small molecules could provide a faster-acting alternative to omalizumab.

Ibrutinib was the first BTK inhibitor approved by the FDA in the United States. Since its initial approval in 2013 for the treatment of mantle cell lymphoma, ibrutinib's therapeutic indications have subsequently been expanded to include various forms of leukemia, lymphoma, and chronic graft-versus-host disease. Ibrutinib is considered the most toxic BTKi due to its marked off-target activity. The most common adverse effects are generally mild and include diarrhea, nausea, skin rash, fatigue, upper respiratory tract infections, edema, and nail changes. However, more serious side effects, such as cytopenias, bleeding, severe infections, and cardiac arrhythmias (such as atrial fibrillation), can lead to treatment discontinuation in approximately 20% of cancer patients. During preclinical development, ibrutinib was shown to potently and comprehensively inhibit IgE-mediated activation of human basophils. In adult patients with peanut and tree nut allergies, ibrutinib has demonstrated promise in removing or lowering mast cell and basophil responses to FAs [49].

In a Phase 2 study of adult patients with peanut allergy, acalabrutinib, a second-generation oral covalent inhibitor of BTK, was shown to be effective in lowering FA responses. Increased thresholds of responsiveness were seen in most patients without any notable adverse consequences [50].

A mouse model study has demonstrated that ruxolitinib is another viable treatment drug for reducing FA symptoms. This study shown that ruxolitinib can considerably lower intestine mast cell hyperplasia, allergen sensitization, and acute anaphylactic symptoms during OFC [51].

Phase I pharmacokinetic data for remibrutinib have been published, showing drug clearance in 12-72 hours depending on the dose, along with a good safety and tolerability profile at all doses.

The evolution of Ibrutinib, remibrutinib has shown promising results in blood and skin pharmacodynamic parameters, with a favorable safety profile (Fig. 3), thus supporting its further development for mast cell, basophil, and B-cell-mediated diseases, such as chronic spontaneous urticaria, allergic asthma, and Sjögren's syndrome [52]. A study of remibrutinib in FA, in subjects with peanut allergy, has been completed, but the results are not yet available. It is anticipated that further research will shed more light on their safety and effectiveness profiles.

2.3 Recombinant monoclonal IgG4(IGX001)

IgG antibodies specific to allergens are necessary for desensitization, although prolonged exposure poses difficulties. Key epitopes on the peanut allergens Arah2 and Arah6 are blocked by recombinant IgG4 monoclonal antibodies such as IGX001. In a mouse model, IGX001 showed protection against intragastric peanut anaphylaxis and mast cell activation. For patients with peanut allergies, it is a promising treatment option that gives quick defense against severe allergic reactions [53].

2.4 PVX108 for peanut allergy

The first peptide-based immunotherapy to be given to patients with FA is PVX108. The seven short peptides that make up PVX108 are immunodominant T-cell epitopes of important peanut allergens. According to the results of a Phase 1 study, PVX108 causes very little activation of peanut-sensitive basophils and is safe and well-tolerated by those with peanut allergies [54]. At this time, there are no clinical ramifications. It is thought to have the potential to be applied to disease modification. Children and adolescents with peanut allergies are presently enrolled in a Phase 2 trial (NCT05621317).

CONCLUSION

With major improvements in treatment choices over the last 10 years, the management of childhood FAs is changing. Omalizumab and OIT are two cutting-edge strategies that are currently gaining popularity and giving patients and their families fresh hope, whereas conventional techniques concentrated on rigorous allergy avoidance. Despite these improvements, obstacles remain, including the need for long-term safety data and accurate biomarkers to determine the efficacy of therapy. Prioritizing tailored care approaches that improve the quality of life for children with FAs is crucial as the field of FA treatment keeps growing.

KEY POINTS

- New treatment approaches, including as oral immunotherapy and omalizumab (licensed by the FDA only), have been approved in clinical practice as alternatives to elimination diets that carry the risk of unintended responses and have demonstrated efficacy in desensitization.

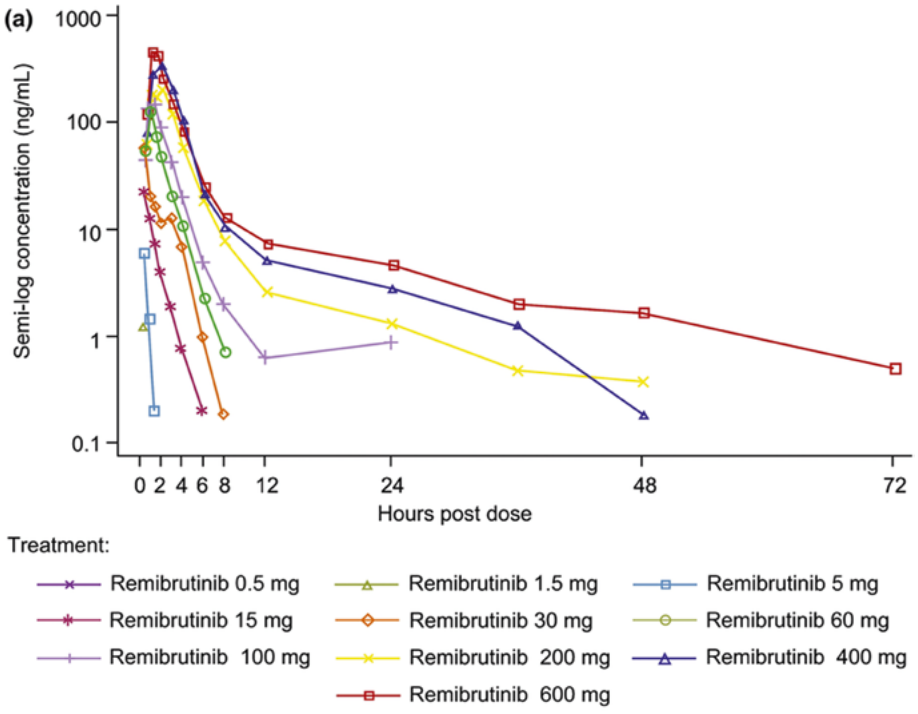


FIGURE 3. Remibrutinib: blood pharmacodynamic parameters (from Kaul M, End P, Cabanski M, et al. Remibrutinib (LOU064): A selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. Clin Transl Sci 2021;14:1756-1768. https://doi.org/10.1111/cts.13005 (CC-BY-NC)) [52].

- Finding reliable biomarkers and standardizing definitions and measurement techniques are essential for enhancing individualized treatment and lessening the substantial impact of food allergies.
- Effective management of this condition requires a collaborative approach that includes patients and their families in the decision-making process.
- Appropriate illness severity categorization and pharmacoeconomic analyses of treatment approaches are also essential for the appropriate allocation of resources.

Funding
No support was necessary.

Informed consent
Not applicable.

Ethics approval
Not applicable.

Consent for publication
All authors approved the final version and its submission.

Disclosure Statement regarding use of generative artificial intelligence (AI) and AI-assisted technologies
Nothing to disclose.

Availability of data and materials
All data supporting the reviews are published.

Declaration of interests
AF has received speaker honoraria and advisory panel consultancy outside the submitted work for Nutricia, Abbott, Danone, Stallergenes, DBV, and Novartis. Funded research (Institution) from Sanofi, Novartis, Ferrero, DBV, GSK, Astrazeneca, Hipp GmBDH, Humana SpA is also declared. SA declares that she has participated as an advisory board member, and/or consultant, and/or speaker/chair at scientific meetings for Aimmune, DBV, Ferrero, Mabylon, Novartis, Stallergenes Greer, Thermo Fisher Scientific and Ulrich outside the submitted work. Funded research (Institution) from Italian Minister of Health and Italian Minister of Education is declared. All other authors have no conflict of interest within the scope of the submitted work.

Conflict of interest disclosure statement

AF declares that he has participated as an advisory board member, and/or consultant, and/or speaker/chair at scientific meetings for Ferrero, Novartis, Sanofi, Stallergenes Greer, outside the submitted work. SA declares that she has participated as an advisory board member, and/or consultant, and/or speaker/chair at scientific meetings for Aimmune, DBV, Ferrero, Mabylon, Novartis, Stallergenes Greer, ThermoFischer Scientific and Ulrich outside the submitted work. Other authors declare no conflict of interest relevant to this publication.

Authors' contributions

All authors contributed to data interpretation and manuscript revision. AF, SA and LD drafted the initial version. VF, AC, RV, CM, LLS, SU, MS, VLT revised and harmonized it. All authors reviewed and approved the final version of the manuscript.

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