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REVIEW

Immunotherapies for food allergy: Exploring new targets and innovative strategies for enhanced efficacy

Jamal Nasser Saleh Al-Maamari[1], Ahmed Al-Qubati[2], Junaidi Khotib[3], Mahardian Rahmadi[3]

[1] Doctoral Programme of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2] Master Programme of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[3] Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

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Correspondence
Junaidi Khotib
Department of Pharmacy Practice
Faculty of Pharmacy
Universitas Airlangga
Indonesia
junaidi-k@ff.unair.ac.id

Abstract

Food allergy is a growing public health concern. It affects children and adults, resulting in significant declines in the overall quality of life. In most cases, individuals must avoid consuming allergenic foods, which can be challenging, especially for patients who experience life-threatening symptoms even with minimal exposure to allergens. This review aimed to identify promising targets for immunotherapy in food allergy, strategies to reduce adverse reactions and side effects, optimal dosing approaches, clinical endpoints to measure efficacy, patient subgroups that benefit, and barriers to implementing immunotherapy. An in-depth literature review was conducted using PubMed and Google Scholar to look into novel approaches and possible targets for enhancing the effectiveness of immunotherapy. Targeting specific immune cells and molecules (e.g. IgE and Tregs), lowering the doses of allergens, extending intervals between doses, personalising dosing, selecting eligible patients carefully, and validating clinical endpoints have shown promising results in overcoming food allergy challenges and increasing immunotherapy efficacy. Potential innovative strategies to enhance immunotherapy efficacy encompass developing more cost-effective approaches, increasing access to trained specialists, developing standardised protocols, and collecting long-term data.

Introduction

Food allergy is a significant public health concern, affecting millions worldwide. Common food allergy symptoms include hives, itching, swelling, vomiting, diarrhoea, and difficulty breathing (Hadley, 2006; Warren *et al.*, 2020; Lopez *et al.*, 2023). Some individuals experience only mild symptoms, while others develop a severe and potentially life-threatening reaction. The exact causes of food allergy are not fully understood but are thought to be a combination of genetic and environmental factors. There is also evidence suggesting that the increasing prevalence of food allergy is due, in part, to changes in dietary habits, environmental factors, and lifestyle (Boden & Wesley Burks, 2011; Turner *et al.*, 2016).

According to recent estimates, food allergy affects approximately 8% of children and 5% of adults in developed countries (Iweala *et al.*, 2018; Westwell-Roper *et al.*, 2022). The only effective treatment for food allergy is strictly avoiding the allergen. However, researchers are exploring novel therapies, including immunotherapy, which involves gradually exposing the individual to increasing doses of the allergen to desensitise the immune system. Although still in its nascent development phase, immunotherapy has exhibited encouraging outcomes in clinical trials, potentially providing a viable alternative for people afflicted with severe food allergies (Arasi *et al.*, 2018; Schoos *et al.*, 2020), holding promise as a potential treatment option for food allergy.

However, adverse reactions are common, particularly during the initial phases of immunotherapy. Thus, this review explores the promising targets for immunotherapy in food allergy, strategies to minimise adverse reactions and side effects, optimal dosing design, clinical benefits, and barriers to implementing immunotherapy.

Promising targets for immunotherapies in food allergy: Effective targeting strategies

While strict avoidance of the allergen is currently the only effective treatment, immunotherapy has been recognised as a potentially effective therapeutic strategy for treating food allergies. The success of immunotherapy is dependent on identifying the most promising targets for immune modulation and developing effective strategies to target them (Hwang *et al.*, 2022; Lloyd *et al.*, 2022).

IgE emerges as a highly promising target for immunotherapy in food allergy. It binds to the allergen, triggering the release of histamine and other mediators that cause the symptoms of an allergic reaction. Targeting IgE is done through monoclonal antibodies, which bind to IgE and prevent its binding to the allergen, and peptides and small molecules, which interfere with the binding of IgE to its receptor on immune cells (Galli & Tsai, 2012; Tontini & Bulfone-Paus, 2021).

Regulatory T cells (Tregs), a specific subset of immune cells responsible for maintaining immunological tolerance, present a promising avenue for immunotherapy in food allergies. Tregs suppress the activation of other immune cells, including those involved in the allergic response. Strategies to target Tregs include the use of recombinant proteins and peptides, which promote the Treg function, and cellular therapies involving the infusion of Tregs into patients (Liu *et al.*, 2021; Palomares *et al.*, 2022).

In addition to targeting specific immune cells and molecules, other promising strategies for immunotherapy in food allergy include probiotics, allergen-specific immunotherapy, and gene therapy. Probiotics modulate the immune response and promote immune tolerance, while allergen-specific immunotherapy involves exposing patients to increasing doses of the allergen to induce immune tolerance. Gene therapy consists of modifying the genetic code of immune cells to enhance their function or reduce their activation in response to an allergen (Pechsrichuang & Jacquet, 2020; Bellinghausen *et al.,* 2022).

Designing immunotherapies to minimise adverse reactions in food allergy

Strategies to minimise the risk of adverse reactions or side effects are critical to the success of immunotherapy in food allergy (Schoos *et al*., 2020; Anagnostou, 2021). One strategy to minimise the risk of adverse reactions is to use modified allergens, which are less likely to trigger an immune response, including recombinant proteins or peptides that lack the epitopes responsible for IgE binding or allergen derivatives that have been chemically modified to reduce their allergenicity. These modified allergens still induce an immune response and promote immune tolerance, but with a reduced risk of adverse reactions (Zhernov *et al.*, 2019; El Mecherfi *et al.*, 2020).

Another strategy is to use slower immunotherapy protocols, which involve lower doses of allergens and longer intervals between doses, allowing the immune system to gradually adapt to the allergen and reducing the risk of severe reactions. Pre-treatment with antihistamines or other medications also reduces the risk of allergic reactions during immunotherapy (Aarestrup *et al.*, 2022).

In addition, careful patient selection and monitoring are critical to minimise the risk of adverse reactions. Patients should undergo thorough allergy testing and evaluation to confirm the diagnosis and identify any potential contraindications to immunotherapy. They should also be closely monitored during and after immunotherapy, with regular assessments of symptoms, vital signs, and laboratory values to detect and manage adverse reactions (Kowalski et al., 2016; Pitsios *et al.*, 2022).

Personalising dosing strategies for immunotherapies in food allergy treatment

One critical consideration in designing an effective immunotherapy regimen is determining the optimal dosing strategy, including the dose, frequency, and duration of treatment. Personalising dosing for individual patients is also critical to maximising the efficacy and safety of immunotherapy (Schoos *et al.*, 2020; Muraro *et al.*, 2022b).

The optimal immunotherapy dosing strategy for food allergy is not well established and varies depending on the allergen, patient characteristics, and treatment goals. However, a growing body of evidence suggests that a gradual increase in the dose of the allergen is a practical approach for inducing immune tolerance and reducing the risk of adverse reactions (Yu *et al.*, 2016;

Feuille & Nowak-Wegrzyn, 2018; Alvaro-Lozano *et al.*, 2020).

One common dosing strategy for allergen-specific immunotherapy is the dosing phase, which involves gradually increasing the allergen dose over weeks to months until the target maintenance dose is reached. This is typically followed by a maintenance phase in which the patient receives regular doses of the allergen at the target dose for several months to years (Song, 2016; Moote *et al.*, 2018).

Personalising dosing for individual patients is also essential to maximise the efficacy and safety of immunotherapy. It is influenced by factors such as the severity of the patient's allergy, age, overall health status, and response to previous treatments. For example, patients with more severe allergies require a more gradual increase in the allergen dose. In contrast, patients with less severe allergies tolerate a more rapid dose escalation (Anderson *et al.*, 2021; Magnan *et al.*, 2023).

Using biomarkers to personalise dosing is also an active research area. Biomarkers such as IgE levels, T cell responses, and cytokine profiles help predict the patient's response to immunotherapy and enable dose adjustment and treatment duration (Breiteneder *et al.*, 2020; Magnan *et al.,* 2023).

Evaluating the efficacy of immunotherapies for food allergy: Relevant clinical endpoints

Evaluating the efficacy of immunotherapies for food allergy is critical to determining the clinical benefits and potential risks of treatment. The evaluation should include subjective and objective measures and patient-reported outcomes for a comprehensive assessment of treatment efficacy (Schoos *et al.*, 2020; Sim *et al.*, 2020). The most relevant clinical endpoints to measure in the evaluation of immunotherapies for food allergy include the following:

Reduction in allergic symptoms

A critical clinical endpoint in evaluating immunotherapies for food allergy is the reduction in allergic symptoms such as urticaria, angioedema, and gastrointestinal and respiratory manifestations. Symptom scores, patient diaries, and physician assessments quantify the severity and frequency of symptoms and evaluate treatment effectiveness in reducing symptoms.

Decrease in medication use

A crucial clinical endpoint is decreased rescue medications, such as epinephrine, antihistamines, and corticosteroids, used to treat acute allergic reactions. Reduced medication use reflects decreased severity and frequency of allergic reactions and provides objective evidence of treatment efficacy.

Improvement in quality of life

The impact of food allergies on quality of life is substantial, with patients experiencing anxiety, social isolation, and reduced productivity. Hence, improving quality of life is a critical clinical endpoint in evaluating immunotherapies for food allergies. Patient-reported outcomes, such as surveys assessing quality of life, can serve as a valuable tool for evaluating the effects of treatment on patient quality of life.

Immunological changes

Changes in immune responses to food allergens, such as reduced allergen-specific IgE levels or increased allergen-specific IgG4 levels, can also be used as a clinical endpoint in evaluating immunotherapies for food allergies. These changes reflect immune tolerance induction and provide objective evidence of treatment efficacy.

Identifying patient subgroups benefiting from immunotherapies in food allergy

There is growing evidence that specific patient subgroups benefit more from immunotherapies for food allergies than others (Canonica *et al.*, 2015; Chang & Sun, 2022). Some examples of these patient subgroups include:

Patients with lower baseline IgE levels

Several studies have suggested that patients with lower baseline IgE levels are more likely to achieve sustained unresponsiveness to food allergens following immunotherapy because these patients have a lower burden of allergen-specific immune cells, making them more amenable to desensitisation and induction of immune tolerance.

Younger patients

Children benefit more from immunotherapy for food allergies than adults due to the potential for more remarkable plasticity in the developing immune system. In addition, younger patients are more likely to

outgrow their food allergy, making immunotherapy a more attractive option for long-term management.

Patients with milder allergy symptoms

Patients with milder food allergy symptoms are more suitable for immunotherapy, as they are less likely to experience adverse reactions and have a better chance of achieving sustained unresponsiveness.

Patients with a single food allergy

Immunotherapy for a single food allergy is simpler and easier to manage than treating multiple food allergies, which require a complex treatment plan for desensitisation to multiple allergens simultaneously. Nonetheless, the effectiveness of immunotherapy varies depending on the number of allergens treated, with individual allergen-targeting potentially more effective. However, multi-food oral immunotherapy is as safe and effective as single-food oral immunotherapy, with benefits varying among individuals based on factors like allergy severity and treatment response.

Patients with high allergen exposure

Patients frequently exposed to their allergen, such as those who have occupational exposure or consume it as part of their regular diet, benefit more from immunotherapy because of the increased risk of exposure to allergic reactions.

Clinical trials and real-world studies should include analyses of treatment outcomes by patient characteristics, such as age, baseline IgE levels, and severity of allergy symptoms, to identify patient subgroups that are more likely to benefit from immunotherapies for food allergies. In addition, the efforts to develop biomarkers to predict treatment response and identify suitable candidates for immunotherapy are ongoing and help further refine patient selection.

Overcoming barriers to implementing food allergy immunotherapy in clinical practice

Despite the promising results of clinical trials supporting immunotherapy for food allergy, several barriers to immunotherapy implementation in clinical practice are mentioned below (Scurlock & Jones, 2010; Muraro *et al.*, 2022a):

Cost

Immunotherapy for food allergies can be expensive, particularly when considering the cost of allergen extracts, administration fees, and monitoring, limiting access to treatment for many patients. One potential solution is to develop more cost-effective approaches to immunotherapy, such as using alternative dosing schedules or developing new formulations that require fewer allergens, which could make immunotherapy affordable, easily accessible, and purchased by patients unable to bear the high costs. Furthermore, using less allergens in immunotherapy reduces the risk of adverse reactions, another benefit of this solution. The risk of adverse reactions decreases by reducing the interaction between the allergen and antigen-presenting cells (APCs). However, further research is needed to determine the optimal dose and formulation of allergen extracts for immunotherapy.

Safety concerns

Immunotherapy can cause adverse reactions, including anaphylaxis, which can be life-threatening. This risk makes some patients and clinicians hesitant to pursue treatment. To address this concern, it is essential to carefully select patients most likely to benefit from immunotherapy and provide rigorous monitoring during treatment to identify and manage adverse reactions.

Limited availability of trained specialists

Immunotherapy for food allergies requires specialised training and expertise, which is unavailable in all clinical settings. One solution is to develop training programmes to increase the number of specialists who can provide this treatment and improve collaboration between specialists and primary care providers to expand access to care.

Lack of standardised protocols

No standardised protocol for immunotherapy for food allergy leads to variability in treatment approaches and outcomes. Developing standardised protocols based on best practices and evidence-based guidelines helps ensure consistency and improve treatment outcomes.

Limited long-term data

While the short-term efficacy of immunotherapy for food allergy has been demonstrated in clinical trials, there is limited data on long-term outcomes and safety. Continued follow-up with patients who have undergone immunotherapy is essential to identify

potential long-term risks and refine treatment protocols.

Conclusion

Food allergy is a significant public health concern, affecting millions worldwide. Immunotherapy has emerged as a promising treatment option for food allergies. This review discussed the most promising targets and strategies to provide effective immunotherapy, for instance, patient subgroups that benefit the most from immunotherapy, and identified the barriers to be implemented in clinical practice, such as cost, safety concerns, the lack of standardised protocols, and limited long-term data. Potential solutions to these challenges were proposed, including developing more cost-effective approaches, increasing access to trained specialists, developing standardised protocols, and collecting long-term data. Further research is needed to provide safe and effective immunotherapy for individuals with food allergies.

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