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The Role of Immunotherapy in the Management of Food Allergy

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ABSTRACT

Food allergy is a health disorder that results from a specific immune response to food. According to the World Allergy Organisation (WAO), 22% of the world's population suffers from allergies, and this number is increasing every year. The increasing morbidity and mortality rates of food allergy cases highlight the need for accurate diagnosis and appropriate treatment. Advances in science and technology have enabled a paradigm shift in allergy prevention, moving from allergen avoidance to desensitisation and active induction of immunological tolerance (immunotherapy). Immunotherapy for food allergy can utilise various routes of administration, including subcutaneous (SCIT), oral (OIT), sublingual (SLIT), intralymphatic (ILIT), and epicutaneous (EPIT). Currently, there are newer formulation approaches that modify the activity of the allergen, improving safety while maintaining effectiveness. The principle of immunotherapy involves gradually increasing exposure to specific allergens, resulting in desensitisation or increased tolerance to these allergens. This article aims to determine the role of immunotherapy in the management of food allergy.

Keywords: Food Allergy, Immunotherapy, Desentization

INTRODUCTION

Food allergy is a health disorder caused by a specific immune response to certain foods, affecting all age groups, including both children and adults. According to the World Allergy Organization (WAO), 22% of the world's population suffers from allergies, a number that continues to increase every year (Wegrzyn et al., 2014). Although the national prevalence of food allergies in Indonesia is not yet established, an epidemiological study in Surabaya reported a prevalence of atopy in school-age children at 61%. A history of atopy, such as atopic dermatitis, can be a risk factor for allergies (Munasir & Muktiarti, 2013). Food allergies in adults may arise from persistent childhood allergies or manifest for the first time in adulthood (Gocki & Bartuzi, 2016).

The term 'food allergy' falls within the category of adverse food reactions. The American Academy of Allergy and the National Institutes of Health categorize adverse food reactions into two parts: food allergy, with an immune mechanism, and food intolerance, with a non-immune mechanism, such as food poisoning (Gocki & Bartuzi, 2016). About 90% of food allergic reactions are caused by peanuts, milk, chicken eggs, soy, fish, shellfish, and wheat (Lopez et al., 2023). Research conducted by Ciborowska and Rudnicka (2010) reported that seafood (fish, shellfish, lobsters, crabs, shrimp), some fruits (cherries, peaches, apricots), and nuts, especially peanuts, are the most common

causes of food allergies in adults.(Ciborowska & Rudnicka, 2010) Gupta et al. (2016) reported an estimated prevalence of food allergies in the United States at around 10.8%, with shellfish being the most common cause (2.9%) (Gupta et al., 2019).

Reactions are influenced by several factors, including hereditary/genetic factors, exposure to allergens, the gastrointestinal tract, and environmental factors (Rengganis & Yunihastuti, 2014). One study reported that twins had a concordance rate of peanut allergy in monozygotic twins (64%) compared to dizygotic twins (7%). This suggests a sevenfold increased risk of developing food allergies if parents or siblings have allergies (Wang & Sampson, 2011). Symptoms vary depending on the mechanism and organs affected, ranging from mild symptoms such as itching to anaphylactic reactions. A 2020 study in the UK showed a hospitalization rate of 4.04 per 10,000 population per year due to food allergy anaphylaxis and a mortality rate ranging from 0.2-0.3 due to laryngeal edema, irreversible bronchospasm, refractory hypotension, or a combination of symptoms (Kam & Raveinal, 2018). Morbidity and mortality can increase in cases of food allergy, emphasizing the need for accurate diagnosis and appropriate management (Kam & Raveinal, 2018; Wegrzyn et al., 2014).

Advances in science and technology allow a paradigm shift from allergen avoidance to desensitization and active induction of immunologic tolerance (Scurlock & Jones, 2010). Immunotherapy involves gradually increasing exposure to specific allergens, expecting a process of desensitization or increased tolerance to occur (Scurlock & Jones, 2010). However, the role of immunotherapy in the management of food allergies has not been widely discussed in theory. Therefore, the author is interested in writing a literature review entitled 'The Role of Immunotherapy in Food Allergy Management.' Understanding this role can contribute to the immediate establishment of a food allergy diagnosis and is expected to facilitate effective management, ultimately reducing morbidity and mortality from food allergies.

IMMUNOTHERAPY

Immunotherapy is a treatment employed by allergists and immunologists, involving a gradual increase in the number of specific allergens until an effective dose is reached. The aim is to induce immunological tolerance to these allergens (Feuille & Nowak-Wegrzyn, 2018). Immunotherapy is applicable across all age groups, although there are special considerations in certain conditions. Research conducted by William Moote et al (2018) highlights specific considerations in administering immunotherapy. For instance, in patients aged less than 6 years, careful consideration is needed due to potential lack of cooperation during the regimen. Similarly, in elderly patients, various comorbidities may influence the decision to implement immunotherapy. Additionally, pregnant women and patients with malignancy or autoimmune disorders/immunodeficiency require special considerations (Feuille & Nowak-Wegrzyn, 2018). Therefore, the decision to proceed with immunotherapy should be made after a thorough evaluation of the risks and benefits associated with the therapy.

MECHANISM OF IMMUNOTHERAPY

The alterations observed in the mechanism of immunotherapy entail changes in immune functions that rely on the response to allergen-specific T cell modifications by inducing regulatory T cells (Tregs) and suppressing Th2 immunity. This process commences with the induction of Foxp3+ Tregs, followed by the uptake of antigens by immature tissue-resident dendritic cells (DC), resulting in DC-mediated Treg induction through the secretion of immunosuppressive cytokines and other mechanisms. These Tregs play a pivotal role in suppressing the allergic response by secreting inhibitory cytokines, namely IL-

10, IL-35, and TGF-ß. Moreover, Tregs express surface receptors that can modify DC function and induce target cell senescence (Akdis & Akdis, 2015; Feuille & Nowak-Wegrzyn, 2018). Immunotherapy triggers a Th2-dominant immune response, leading to a reduced production of allergen-specific Th2 cytokines. Th1 cytokines, such as IFN-Ɣ, can selectively inhibit Th2 immunity and IgE production.

In allergen-specific immunotherapy, dendritic cells capture allergens and migrate to regional lymph nodes. This initiates the induction of naive T cells into regulatory T cells (Tregs) through allergen presentation on MHC, along with the secretion of cytokines like TGF-ß, retinoic acid, indoleamine 2,3-dioxygenase, and other mechanisms. The secretion of cytokines IL-10 and TGF-ß suppresses Th2 immunity and mast cell reactivity, reducing IgE synthesis while increasing IgG and IgA synthesis. IFN-Ɣ production by TH1 cells suppresses the TH2 response and reduces IgE. Additionally, another potential mechanism involves the anergy/apoptosis of Th2 cells due to persistent antigen stimulation (Akdis & Akdis, 2015; Feuille & Nowak-Wegrzyn, 2018). Research by Lichtenstein et al demonstrated that the success of immunotherapy relies on the induction of an IgG response, particularly with IgG4 playing a crucial role. IgG1 appears in the early phase of immunotherapy, while significant production of IgG4 occurs after long-term treatment. Therefore, the IgE to IgG4 ratio can be considered (Akdis & Akdis, 2015). This mechanism is illustrated in Figure 2.

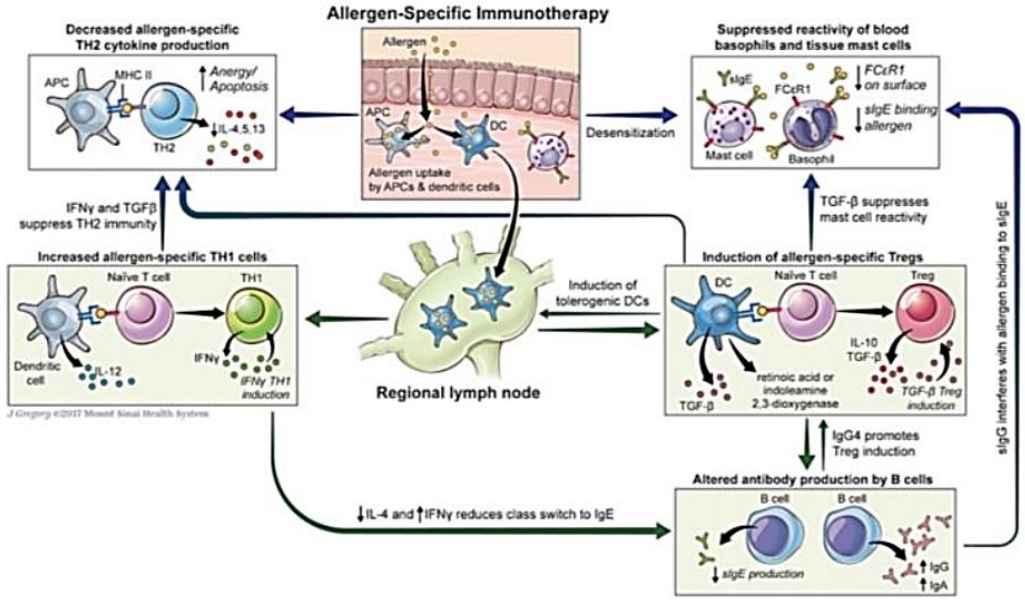

Figure 2. Mechanism of Tolerance Induction in Allergen-Spesific Immunotherapy (Feuille & Nowak-Wegrzyn, 2018)

IMMUNOTHERAPY APPROACH

Immunotherapy for food allergies can utilize various routes of administration, such as subcutaneous (SCIT), oral (OIT), sublingual (SLIT), intralymphatic (ILIT), and epicutaneous (EPIT). Earlier studies on subcutaneous immunotherapy for peanut allergy demonstrated the potential for desensitization. However, due to safety concerns associated with drug effects, most experts opted to discontinue SCIT. Oral immunotherapy (OIT) has emerged as the most effective approach to date (Tophof et al., 2017). Figure 3 illustrates several immunotherapy approach.

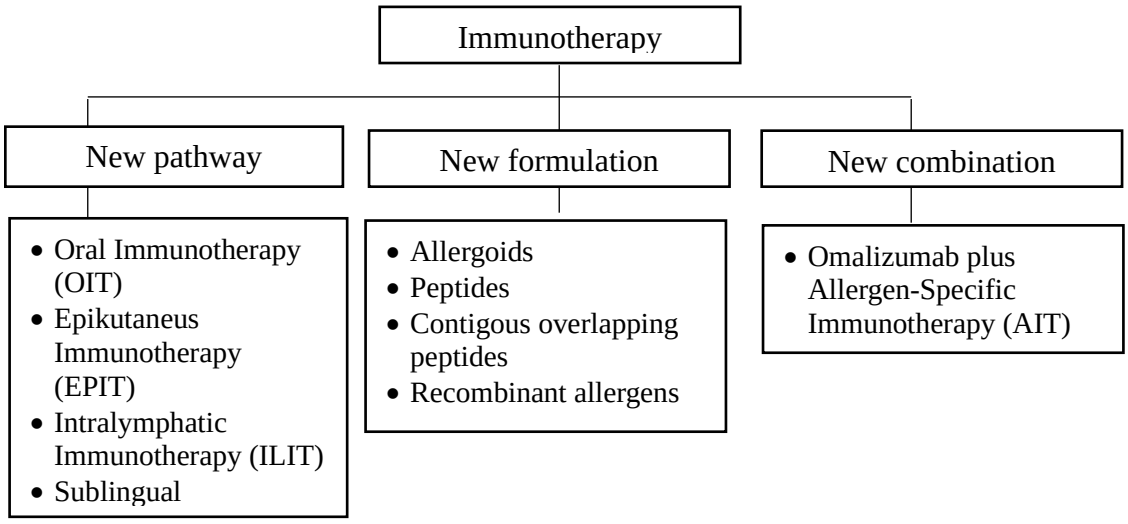

Figure 3. Allergen Immunotherapy Approach

1. New pathway approach

a. Oral Immunotherapy (OIT)

Oral Immunotherapy (OIT) involves the use of food as an allergen, gradually consumed with increasing doses. Induction of desensitization to food allergens such as milk, eggs, and peanuts has been observed in clinical trials (Gaur, 2018). OIT operates through the underlying mechanism of oral tolerance, suppressing allergic responses, as illustrated in Figure 4.

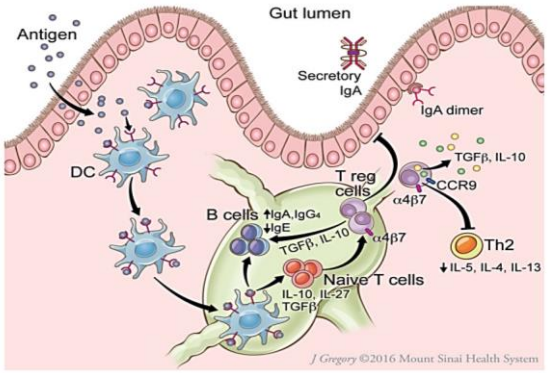

Figure 4. Mechanism of Inducing Oral Tolerance in the Intestines (Gaur, 2018)

Oral tolerance relies on the induction of Regulatory T cells (Tregs) within the lymphoid tissue in the intestines. Antigens enter the lamina propria dendritic cells (DCs) via goblet cells, and antigen uptake occurs by CD103+ DCs in the lamina propria of the intestine. Subsequently, these DCs migrate to the mesenteric lymph nodes, where interactions with T lymphocytes in the intestines take place. Regulatory B cells also play a role in this induction. Research indicates that Oral Immunotherapy (OIT) can reduce the diameter of the skin prick test (SPT), decrease basophil reactivity, lower specific antigen IgE levels, and increase IgG and IgA. This also leads to a reduction in Th2 cytokine production (IL-4 and IL-13), increased production of specific Th1 allergen (IFN-Ɣ), and Treg cytokines (TGF-Ɣ) (Kim & Burks, 2020). The Oral Immunotherapy (OIT) dosing protocol consists of three phases, including (1) the escalation phase – conducted in one day or more, with a rapid increase in dosage, typically ranging from 10-25 mg at a maximum, (2) the dose build-up phase – usually carried out at home with dosage increments every two weeks or more,

ranging from 300 mg to 4000 mg, and (3) the maintenance phase – which can extend from months to years (Akdis & Akdis, 2015). The OIT approach can be observed in Figure 5.

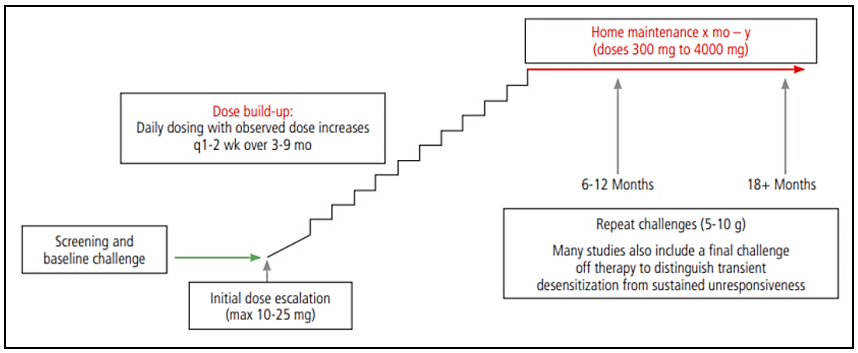

Figure 5. Approach to Oral Immunotherapy (Wood, 2017)

The study conducted by Buchanan et al. (2007) on children with egg allergies involved a 24-month Oral Immunotherapy (OIT) treatment. The results revealed that 4 out of 7 children who successfully completed the study were able to tolerate a high dose of egg protein, specifically 10 grams of egg, by the end of the therapy (Buchanan et al., 2007). However, in another study conducted by Burks et al., it was reported that 2 out of 21 individuals participating in the research were unable to reach the egg protein dose during the maintenance phase due to side effects or adverse reactions. Therefore, ongoing research is still being conducted to further investigate the safety, efficacy, and mechanisms of Oral Immunotherapy (OIT) (Gaur, 2018). The current weaknesses of the Oral Immunotherapy (OIT) protocol include the occurrence of potential side effects, low tolerability, the need for intensive time and effort, and the requirement for close monitoring and involvement from both doctors and family members (Gaur, 2018).

b. Immunotherapy Epicutaneous (EPIT)

The principle of Epicutaneous Immunotherapy (EPIT) is to administer allergens to the nonvascularized epidermal area to reduce the risk of allergens reaching the bloodstream. The reason for choosing the EPIT route is that the highest number of antigen-presenting cells (APC) is located in the skin. Keratinocytes can be activated, enhancing immunogenicity (Scurlock et al., 2021). The research conducted by Kim et al using cow's milk allergen indicates that Epicutaneous Immunotherapy (EPIT) is well-tolerated without systemic anaphylactic reactions. However, a significant increase in vulnerability to eczema on the skin needs to be observed (Kim & Burks, 2020). The current limitations of EPIT are as follows: the allergen dosage applied to the skin can easily exceed a certain concentration, it involves costs, and damaged skin may pose a risk of systemic allergic effect (Kim & Burks, 2020). The EPIT method can be demonstrated in Figure 5.

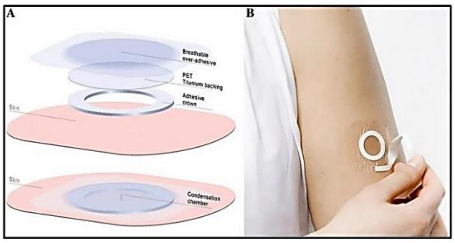

Figure 5. Administration of Epicutaneous Immunotherapy (EPIT) (Dupont et al., 2010)

Comparison between Oral Immunotherapy (OIT) and Epicutaneous Immunotherapy (EPIT) methods can show in figure 6.

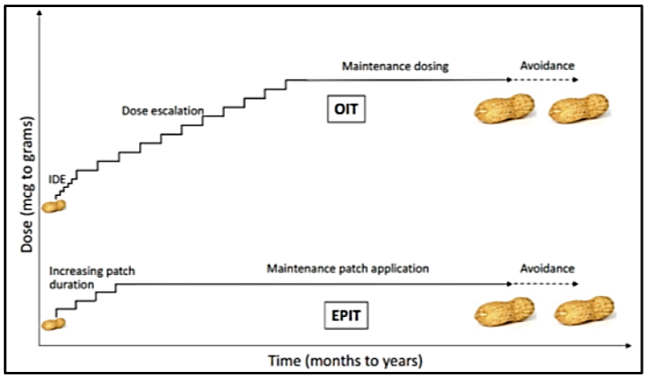

Figure 6. Differences between OIT and EPIT (Scurlock et al., 2021)

c. Immunoterapi Intralymphatic (ILIT)

Intralymphatic Immunotherapy (ILIT) is performed by injecting allergens directly into the inguinal lymph nodes under ultrasound guidance. The advantages of using the ILIT route include lower allergen doses compared to other routes, increased patient compliance, and proven good tolerance. Research conducted by Simon and Namazy (2018) on patients with nut allergies revealed that systemic reactions occurred to ILIT doses, but these reactions could be prevented with a pretreatment protocol involving oral antihistamines, short-acting beta-agonists, leukotriene modifiers, and oral corticosteroids. The results of this study indicated that patients experienced dose tolerance and a decrease in skin prick test reactivity to nut extracts (Simon & Namazy, 2019). ILIT also has some limitations, including: adverse reactions can be triggered due to leakage of allergens from the lymph nodes, limited amounts of allergen, and limitations in knowledge regarding efficacy, safety, and mechanisms of action (Simon & Namazy, 2019).

d. Sublingual Immunotherapy (SLIT)

The mechanism of action of Sublingual Immunotherapy (SLIT) can trigger IgE, IgG4, and cytokines secreted by Treg and Th2 cells. Dendritic cells and Langerhans cells in the oral mucosa can induce the emergence of Treg cells and IL-10 cytokines. The advantages of using the SLIT approach include rarely encountering SLIT side effects because in the oral mucosa, immune effector cells are found in small numbers, and food allergen proteins used will not be degraded by stomach enzymes as the site of allergen exposure is sublingual (Narisety & Keet, 2012). SLIT is performed by placing liquid extracts of food allergens in small doses (starting from micrograms to milligrams) under the sublingual area, beneath the tongue. The duration of SLIT therapy may be shorter compared to Oral Immunotherapy (OIT) because the target dose achievement in SLIT is lower than in OIT (Narisety & Keet, 2012).

2. New formulation approach

a. Allergoids

Allergoids are modified allergens designed to reduce allergenic activity. The use of allergoids is inspired by Lowenstein, who deactivated the toxic activity of tetanus toxin using formaldehyde, resulting in an immunogenic product. This concept was first claimed by Carter in the Abbott laboratories in the United States (Olivier, 2017). The principle is that allergoids have less reactive B-cell epitopes, reducing IgE binding (enhancing safety), while retaining T-cell epitopes without altering their immunogenic effect (maintaining efficacy). Survey results report that allergoids contribute up to 50% of Subcutaneous

Immunotherapy (SCIT) (Rajakulendran et al., 2018). Several studies indicate that the use of allergoids can shorten the duration of immunotherapy (Olivier, 2017).

The study conducted by Smit et al. (2013) aimed to identify the safety and effectiveness of using allergoid peanut extract (modified/ mPE peanut extract) in rats, comparing it with exposure to peanut extract (PE). The research showed that both PE and mPE induced specific IgG antibodies in rats, but rats exposed to PE experienced severe anaphylactic symptoms. This did not occur in rats exposed to mPE. This indicates that the use of allergoids has better safety while still maintaining its immunogenicity and effectiveness (Smit et al., 2013).

b. Peptides

Short soluble synthetic peptides contain specific CD4 T-cell epitopes of allergens that induce tolerance by stimulating regulatory T cells (Treg) and Th1 cells. The principle is a reduction in the ability to crosslink IgE and the maintenance of the ability to modulate specific allergen-specific T cells. Peptide immunotherapy is currently being developed as a treatment for allergies and autoimmune conditions where the pathogenesis relies on T cells. The advantages of peptides include shortening the duration of therapy and demonstrating a higher level of safety (Gocki & Bartuzi, 2016).

An advanced study evaluated two Cat-Peptide Antigen Desensitisation (Cat-PAD) immunotherapy regimens in 202 patients with cat allergies. Patients received 6 nanomolar injections of Cat-PAD every 4 weeks (a total of 4 injections). Subsequently, for four consecutive days, patients entered an exposure chamber to determine if the therapy was effective in treating rhino-conjunctivitis symptoms. The results of the study showed that patients given Cat-PAD immunotherapy experienced a reduction in persistent symptoms one year after the four injections. This suggests that synthetic peptides can be an easier immunotherapy strategy without the need for dose escalation, and their benefits can last up to one year (Patel et al., 2013).

c. Contiguous Overlapping Peptides

Contiguous Overlapping Peptides (COP) is a recombinant allergen in specific allergen immunotherapy. COP encompasses the entire allergen sequence, generating potential T-cell epitopes, while preventing IgE conformational epitopes on the original allergen. A study conducted by Pellaton et al. (2013) evaluated the hypoallergenicity of COP in vitro and in vivo. The results of the study indicate that the specific allergen immunotherapy strategy using COP injections can be applied to patients with pollen sensitivity. Research conducted on mice and humans showed limited binding of COP to IgE. The use of COP is safe after subcutaneous injection in sensitive mice, does not induce anaphylactic reactions, does not activate basophils in human experiments, and does not induce reactions in prick tests (Pellaton et al., 2013).

d. Recombinant Allergens

Recombinant allergens contain T-cell and IgE epitopes from the allergen and can induce the blocking/inhibition of specific allergen IgG antibodies through immunization and T-cell tolerance. An article written by Zhernov et al. (2019) indicates that several strategies for Allergen-Specific Immunotherapy (AIT) have been developed. In clinical trials of AIT, therapy using recombinant and synthetic derivatives of allergens can induce specific allergen IgG antibodies and interfere with the recognition of allergens by IgE. Immunotherapy with recombinant allergen-specific IgG monoclonal antibodies can reduce allergic symptoms. A further molecular approach is preventing allergies through vaccination using hypoallergenic recombinant allergen derivatives (Zhernov et al., 2019).

3. New recombinant

Omalizumab has been used in the therapy of asthma and chronic idiopathic urticaria. In food allergies, the use of omalizumab in Oral Immunotherapy (OIT) has led to a reduction in the required duration to achieve maintenance doses and side effects. A study conducted by MacGinnitie et al. (2017) on patients aged 6-19 years with peanut allergies consisted of two groups: the intervention group receiving omalizumab and the control group not receiving omalizumab. The study showed that 79% of the intervention group achieved tolerance in high-dose OIT (MacGinnitie et al., 2017).

INDICATIONS AND CONTRAINDICATIONS OF IMMUNOTHERAPY

The procedure performed when initiating immunotherapy involves the patient undergoing an examination to determine allergic reactions, namely through a skin test. During the skin test procedure, allergens are injected and observed for 15 minutes. If redness and swelling occur, it indicates an allergic reaction to the injected allergen. Subsequently, the doctor ensures the patient's condition before administering immunotherapy and determines the suitable immunotherapy approach for the patient. Specific allergen immunotherapy is indicated for patients with allergic rhinitis/conjunctivitis, asthma, or food allergies who have evidence of specific allergen IgE antibodies, especially in patients requiring high-dose treatment and/or multiple medications to maintain disease control, experiencing medication side effects, or avoiding long-term pharmacological therapy (Akdis & Akdis, 2015; Moote et al., 2018).

Multicenter phase III clinical trials are still ongoing to conduct research on Oral Immunotherapy (OIT) and Epicutaneous Immunotherapy (EPIT). What is needed is to establish an effective and safe minimum maintenance phase dose, minimum maintenance phase duration, therapy duration, and maintenance dose frequency as long-term treatment. Approaches to reduce the side effects of immunotherapy and the development of oral tolerance, such as adjuvants, DNA vaccines, or combination therapies, need to be further explored (Pajno et al., 2014).

Immunotherapy is contraindicated in patients with medical conditions that pose a risk of death, such as uncontrolled asthma or cardiovascular diseases (unstable angina, recent myocardial infarction, arrhythmia, and uncontrolled hypertension). Patients receiving beta-blocker and ACE inhibitor therapy are contraindicated for immunotherapy (Gaur, 2018; Moote et al., 2018). The study conducted by Nassiri et al. (2015) indicates that the combination of ß-blocker and ACE inhibitor administration can worsen anaphylaxis symptoms as it may increase histamine release from mast cells mediated by FcεRI (Nassiri et al., 2015).

Immunotherapy can have several side effects, including local reactions, systemic reactions, and anaphylactic reactions. Local reactions occur in the vicinity of the allergen entry site, presenting with redness, irritation, and swelling at the injection site in Subcutaneous Immunotherapy (SCIT), and they typically resolve on their own. Local reactions are generally mild. A study conducted by Tophof et al. (2017) showed that 54.6% of patients experienced local side effects such as inflammation, itching at the injection site, and 2.2% of patients experienced systemic side effects in those undergoing SCIT (Tophof et al., 2017).

CONCLUSION

Immunotherapy is a food allergy treatment that involves gradually increasing exposure to specific allergens to induce desensitization and tolerance. Immunotherapy can be classified into SCIT, OIT, SLIT, EPIT, and ILIT, with OIT being a widely used approach today. Indications for immunotherapy include patients with specific allergen IgE antibodies, especially those requiring high-dose treatment and/or multiple medications to maintain disease control, experiencing medication side

effects, and avoiding long-term pharmacological therapy. Immunotherapy is contraindicated in patients with uncontrolled asthma or cardiovascular diseases (unstable angina, recent myocardial infarction, arrhythmia, and uncontrolled hypertension), as well as patients receiving beta-blocker and ACE inhibitor therapy. Possible side effects of immunotherapy include local reactions, systemic reactions, and anaphylaxis. Therefore, the development of immunotherapy in managing food allergies requires consideration of resource availability and the tools or materials used in the preparation and implementation of immunotherapy procedures.

Declaration by Authors

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REFERENCES

1. Akdis, C., & Akdis, M. (2015). Advances in allergen immunotherapy: Aiming for complete tolerance to allergens. *Science Translational Medicine*, *7*(280).
2. Astier, C., Morisset, M., Roitel, O., Codreanu, F., Jacquenet, S., Franck, P., Ogier, V., Petit, N., Proust, B., Moneret-Vautrin, D. A., Burks, A. W., Bihain, B., Sampson, H. A., & Kanny, G. (2006). Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J. Allergy Clin. Imunol*, *118*(1), 250–256. https://doi.org/10.1016/j.jaci.2006.04.053
3. Boyce, J., Assa'ad, A., Burks, W., Jones, S., Sampson, H., Wood, R., Plaut, M., Cooper, S. F., & Fenton, M. J. (2010). Guidelines for the diagnosis and management of food allergy in the United States. *J. Allergy Clin. Imunol*, *126*(6), 1–85. https://doi.org/10.1016/j.jaci.2010.10.007
4. Buchanan, A. D., Green, T. D., Jones, S. M., Scurlock, A. M., Christie, L., Althage, K. A., Steele, P. H., Pons, L., Helm, R. M., Lee, L. A., & Burks, A. W. (2007). Egg oral immunotherapy in nonanaphylactic children with egg allergy. *Journal of Allergy and Clinical Immunology*, *119*(1), 199–205. https://doi.org/10.1016/j.jaci.2006.09.016
5. Ciborowska, H., & Rudnicka, A. (2010). Dietetics: nutrition healthy and sick man. *Medical Publisher*.
6. Dupont, C., Kalach, N., Soulaines, P., Morillon, S. L., Piloquet, H., & Benhamou, P. H. (2010). Cow's milk epicutaneous immunotherapy in children: A pilot trial of safety, acceptability, and impact on allergic reactivity. In *Journal of Allergy and Clinical Immunology* (Vol. 125, Issue 5, pp. 1163–1165). https://doi.org/10.1016/j.jaci.2010.02.015
7. Feuille, E., & Nowak-Wegrzyn, A. (2018). Allergen-specific immunotherapies for food allergy. In *Allergy, Asthma and Immunology Research* (Vol. 10, Issue 3, pp. 189–206). Korean Academy of Asthma, Allergy and Clinical Immunology. https://doi.org/10.4168/aair.2018.10.3.189
8. Gaur, S. (2018). Future modalities in allergen immunotherapy: A brief overview. *Indian Journal of Allergy, Asthma and Immunology*, *32*(2), 43. https://doi.org/10.4103/ijaai.ijaai_20_18
9. Gocki, J., & Bartuzi, Z. (2016). Role of immunoglobulin G antibodies in diagnosis of food allergy. In *Adv dermatol allergol* (Vol. 33, Issue 4, pp. 253–256). Termedia Publishing House Ltd. https://doi.org/10.5114/ada.2016.61600
10. Gupta, R. S., Warren, C. M., Smith, B. M., Jiang, J., Blumenstock, J. A., Davis, M. M., Schleimer, R. P., & Nadeau, K. C. (2019). Prevalence and Severity of Food Allergies Among US Adults. *JAMA Network Open*, *2*(1), e185630. https://doi.org/10.1001/jamanetworkopen.2018.5630
11. Ho, M., Wong, W., & Chang, C. (2014). Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol*, *46*(3), 225–240.
12. Kam, A., & Raveinal. (2018). Imunopatogenesis dan Implikasi Klinis Alergi Makanan pada Dewasa. *Jurnal Kesehatan Andalas*, *7*, 144–151. http://jurnal.fk.unand.ac.id
13. Kim, E. H., & Burks, A. W. (2020). Food allergy immunotherapy: Oral immunotherapy and epicutaneous immunotherapy. In *Allergy: European Journal of Allergy and Clinical Immunology* (Vol. 75, Issue 6, pp. 1337–1346).

Blackwell Publishing Ltd. https://doi.org/10.1111/all.14220
14. Levani, Y. (2022). *Angioderma*. Alomedika. https://www.alomedika.com/penyakit/alergi-dan-imunologi/angioedema
15. Lopez, C. M., Yarrarapu, S. N. S., & Mendez, M. D. (2023). Food allergies. *Statpearls Publishing*, 1–34.
16. MacGinnitie, A. J., Rachid, R., Gragg, H., Little, S. V., Lakin, P., Cianferoni, A., Heimall, J., Makhija, M., Robison, R., Chinthrajah, R. S., Lee, J., Lebovidge, J., Dominguez, T., Rooney, C., Lewis, M. O., Koss, J., Burke-Roberts, E., Chin, K., Logvinenko, T., … Schneider, L. C. (2017). Omalizumab facilitates rapid oral desensitization for peanut allergy. *Journal of Allergy and Clinical Immunology*, *139*(3), 873-881.e8. https://doi.org/10.1016/j.jaci.2016.08.010
17. Moote, W., Kim, H., & Ellis, A. K. (2018). Allergen-specific immunotherapy. In *Allergy, Asthma and Clinical Immunology* (Vol. 14, Issue 2, pp. 53–62). BioMed Central Ltd. https://doi.org/10.1186/s13223-018-0282-5
18. Munasir, Z., & Muktiarti, D. (2013). The management of food allergy in Indonesia. *Asia Pacific Allergy*, *3*(1), 23–28. https://doi.org/10.5415/apallergy.2013.3.1.23
19. Narisety, S. D., & Keet, C. A. (2012). Sublingual vs oral immunotherapy for food allergy: Identifying the right approach. In *NIH Public Access* (Vol. 72, Issue 15, pp. 1977–1989). https://doi.org/10.2165/11640800-000000000-00000
20. Nassiri, M., Babina, M., Dölle, S., Edenharter, G., Ruëff, F., & Worm, M. (2015). Ramipril and metoprolol intake aggravate human and murine anaphylaxis: Evidence for direct mast cell priming. *Journal of Allergy and Clinical Immunology*, *135*(2), 491–499. https://doi.org/10.1016/j.jaci.2014.09.004
21. Olivier, C. E. (2017). The use of Allergoids and Adjuvants in Allergen Immunotherapy. *Archives of Asthma, Allergy and Immunology*, *1*(1), 040–060. https://doi.org/10.29328/journal.haard.1001006
22. Pajno, G. B., Cox, L., Caminiti, L., Ramistella, V., & Crisafulli, G. (2014). Oral immunotherapy for treatment of immunoglobulin E-mediated food allergy: The transition to clinical practice. In *Pediatric, Allergy, Immunology, and Pulmonology* (Vol. 27, Issue 2, pp. 42–50). Mary Ann Liebert Inc. https://doi.org/10.1089/ped.2014.0332
23. Patel, D., Couroux, P., Hickey, P., Salapatek, A. M., Laidler, P., Larché, M., & Hafner, R. P. (2013). Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: A randomized, placebo-controlled study. *Journal of Allergy and Clinical Immunology*, *131*(1). https://doi.org/10.1016/j.jaci.2012.07.028
24. Pellaton, C., Perrin, Y., Boudousquié, C., Barbier, N., Wassenberg, J., Corradin, G., Thierry, A. C., Audran, R., Reymond, C., & Spertini, F. (2013). Novel birch pollen specific immunotherapy formulation based on contiguous overlapping peptides. *Clinical and Translational Allergy*, *3*(1), 1–11. https://doi.org/10.1186/2045-7022-3-17
25. Rajakulendran, M., Tham, E. H., Soh, J. Y., & Van Bever, H. P. (2018). Novel strategies in immunotherapy for allergic diseases. *Asia Pacific Allergy*, *8*(2), e14. https://doi.org/10.5415/apallergy.2018.8.e14
26. Rengganis, I., & Yunihastuti, E. (2014). Alergi makanan. In S. Setiati, I. Alwi, A. W. Sudoyo, M. Simadibrata, B. Setiyohadi, & A. F. Syam (Eds.), *Buku Ajar Ilmu Penyakit Dalam* (Vol. 1, pp. 508–512). Interna Publishing.
27. Saito-Abe, M., Yamamoto-Hanada, K., Pak, K., Iwamoto, S., Sato, M., Miyaji, Y., Mezawa, H., Nishizato, M., Yang, L., Kumasaka, N., Kobayashi, T., & Ohya, Y. (2022). How a Family History of Allergic Diseases Influences Food Allergy in Children: The Japan Environment and Children's Study. *Nutrients*, *14*(20), 1–11. https://doi.org/10.3390/nu14204323
28. Scurlock, A. M., Burks, A. W., Sicherer, S. H., Leung, D. Y. M., Kim, E. H., Henning, A. K., Dawson, P., Lindblad, R. W., Berin, M. C., Cho, C. B., Davidson, W. F., Plaut, M., Sampson, H. A., Wood, R. A., & Jones, S. M. (2021). Epicutaneous immunotherapy for treatment of peanut allergy: Follow-up from the Consortium for Food Allergy Research. *Journal of Allergy and Clinical Immunology*, *147*(3), 992-1003.e5. https://doi.org/10.1016/j.jaci.2020.11.027

29. Scurlock, A. M., & Jones, S. M. (2010). An update on immunotherapy for food allergy. *Curr Opin Allergy Clin Immunol*, *10*(6), 587–593. https://doi.org/10.1097/ACI
30. Simon, R. A., & Namazy, J. A. (2019). Intralymphatic Immunotherapy for Peanut Allergy: A pilot study of three patients. *Journal of Allergy and Clinical Immunology*, *143*(2), AB255. https://doi.org/10.1016/j.jaci.2018.12.780
31. Smit, J., Pieters, R., van Roest, M., Kruijssen, L., Koppelman, S., Opstelten, D.-J., & Van der Kleij, H. (2013). A novel peanut allergoid is safe and effective in immunotherapy in a peanut allergy mouse model. *Clinical and Translational Allergy*, *3*(S3). https://doi.org/10.1186/2045-7022-3-s3-p1
32. Ta, V., Weldon, B., Yu, G., Humblet, O., Neale-May, S., & Nadeau, K. (2011). Use of specific IgE and skin prick test to determine clinical reaction severity. *Br J Med Med Res*, *1*(4), 410–429.
33. Tophof, M. A., Hermanns, A., Adelt, T., Eberle, P., Gronke, C., Friedrichs, F., Knecht, R., & Monter, E. (2017). Side effects during subcutaneous immunotherapy in children with allergic diseases. *Pediatric Allergy and Immunology*.
34. Torgerson, T. R. (2007). Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: Forkhead box protein 3 mutations and lack of regulatory T cells. *The Journal of Allergy and Clinical Immunology*, *120*(4), 744–750.
35. Wang, J., & Sampson, H. A. (2011). Food allergy. In *Journal of Clinical Investigation* (Vol. 121, Issue 3, pp. 827–835). https://doi.org/10.1172/JCI45434
36. Wegrzyn, A. N., Burks, W., & Sampson, H. A. (2014). Reactions to foods. In F. Adkinson, B. Bochner, W. Burks, W. Busse, S. Holgate, R. Lemanske, & R. Hehir (Eds.), *Middleton's allergy principles & practice* (Vol. 2, pp. 1310–1336). elsevier.
37. Wood, R. (2017). Oral Immunotherapy for Food Allergy. *J Investig Allergol Clin Immunol*, *27*(3), 151–159.
38. Zhernov, Y., Curin, M., Khaitov, M., Karaulov, A., & Valenta, R. (2019). Recombinant allergens for immunotherapy: State of the art. *Current Opinion in Allergy and Clinical Immunology*, *19*(4), 402–414

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