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PRACA POGLĄDOWA
REVIEW

Allergen immunotherapy as a form of preventing the development of allergies: A literature review

Immunoterapia alergenowa jako forma zapobiegania rozwojowi alergii – przegląd piśmiennictwa

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ABSTRACT

Allergen immunotherapy (AIT) shows great promise not only in treating allergies but also in preventing the development of new allergic conditions, which has recently gained scientific attention. The aim of this review is to summarize current knowledge on how AIT modulates immune responses and its potential as a preventive tool for allergic diseases. By targeting the underlying immunological mechanisms, AIT offers the possibility of not only alleviating symptoms but also preventing the progression of new allergies. This review is based on literature published in English, sourced mainly from PubMed and Google Scholar. Only full-text original studies, reviews, and meta-analyses were included. Animal studies, conference abstracts, and non-peer-reviewed content were excluded. AIT reshapes immune responses by shifting from Th2 dominance to a more balanced Th1/regulatory pattern. This includes reduced IgE production, increased IgG4, and limited activation of effector cells. Some studies have shown AIT reduces the risk of new sensitization in children and adults, although results vary depending on allergen type, patient age, and treatment method. AIT appears to be a promising strategy for allergy prevention, offering more durable and disease-modifying effects than other methods such as elimination diets, probiotics, or allergen avoidance. However, more research is needed to define its optimal use, ensure long-term safety, and personalize treatments based on individual risk profiles.

KEYWORDS

allergy, immune system, allergen immunotherapy, immune tolerance, allergy prevention

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STRESZCZENIE

Immunoterapia alergenowa (*allergen immunotherapy* – AIT) ma duży potencjał nie tylko w leczeniu alergii, ale także w zapobieganiu rozwojowi nowych schorzeń alergicznych. Celem pracy jest przedstawienie aktualnego stanu wiedzy na temat roli AIT w modyfikowaniu odpowiedzi immunologicznej i zapobieganiu nowym alergiom. Przegląd oparto na literaturze naukowej w języku angielskim, pochodzącej głównie z baz PubMed i Google Scholar. Uwzględniono pełnotekstowe artykuły oryginalne, przeglądowe oraz metaanalizy. Wykluczono badania na zwierzętach, abstrakty konferencyjne oraz materiały nierecenzowane. AIT modyfikuje odpowiedź immunologiczną poprzez przesunięcie z dominacji limfocytów Th2 w kierunku odpowiedzi Th1 i wzrost liczby komórek regulatorowych T. Dzięki temu dochodzi do zmniejszenia produkcji IgE, zwiększenia produkcji IgG4 i ograniczenia aktywności komórek efektorowych. Immunoterapia ma potencjał w zapobieganiu rozwojowi nowych uczuleń, choć dane są częściowo niespójne. Wykazano korzyści u dzieci i dorosłych, lecz skuteczność różni się w zależności od rodzaju alergenu, wieku i metody leczenia. AIT jest obiecującą strategią w zapobieganiu alergiom, oferującą trwalsze i bardziej skuteczne efekty niż inne metody, takie jak diety eliminacyjne, probiotyki czy unikanie alergenów. Konieczne są jednak dalsze badania w celu ustalenia optymalnego czasu rozpoczęcia terapii, zapewnienia długoterminowego bezpieczeństwa oraz indywidualnego dostosowania leczenia do potrzeb pacjenta.

SŁOWA KLUCZOWE

alergia, układ odpornościowy, immunoterapia alergenowa, tolerancja immunologiczna, prewencja alergii

Introduction

Allergen immunotherapy (AIT) originated in 1911 when Leonard Noon introduced a novel treatment for hay fever, which involved administering gradually increasing doses of a crude grass pollen extract [1]. Unlike symptomatic treatments, AIT involves an etiological intervention aimed at the underlying pathophysiology of allergic disorders, exerting its effects through the modulation of core immunological pathways and promoting the establishment of long--term immune tolerance [2]. Recently, a new approach to AIT has been investigated, which is its efficacy in the context of the prevention of the development of new allergies [3].

It is estimated that in 2019, 33% of citizens of Europe experienced allergic manifestations. In Poland, allergies represent an increasing public health concern, with approximately 40% of the population displaying allergy symptoms, including 12% diagnosed with asthma [4]. Allergy, defined as an exaggerated immune response to harmless environmental substances, can cause symptoms ranging from skin reactions and breathing difficulties to gastrointestinal issues and, in severe cases, cardiovascular collapse [5]. Beyond physical symptoms, allergies can impair sleep, school, and work performance, reducing overall quality of life [6]. Moreover, allergies impose substantial economic costs on both patients and society [7]. Since allergies often begin early in life and persist into adulthood, with many patients developing multiple allergic diseases over time, new strategies for prevention, like AIT, are urgently needed.

The aim of this paper is to present the current state of knowledge on the role of immunotherapy in modulating the immune response and preventing the development of new allergies.

Review methods

This review aims to answer the following question: Is AIT an effective method for preventing the development of new sensitizations in patients with pre-existing allergic diseases?

The inclusion criteria for this review were as follows: original studies (randomized controlled trials, cohort studies, or observational studies) and meta-analyses published in English, with full-text availability online. The study population included both children and adults. The intervention of interest was AIT, specifically subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Eligible studies were required to evaluate the development of new sensitizations as an outcome, with a minimum treatment and follow-up duration of three years.

Exclusion criteria encompassed studies conducted exclusively on animals or in vitro, as well as non-peer--reviewed publications such as conference abstracts, commentaries, and letters to the editor. Studies that did not clearly define outcomes related to the development of sensitization or had a follow-up period shorter than three years were also excluded. Articles published in languages other than English were excluded unless a full-text English translation was available.

A comprehensive literature search was conducted using electronic databases including PubMed, Google Scholar, and Scopus, as well as journal articles from the publisher MDPI (Multidisciplinary Digital Publishing Institute). The search strategy followed the PICO framework:

- Population (P): Patients with allergic diseases
- Intervention (I): Allergen immunotherapy
- Comparison (C): No immunotherapy or placebo
- Outcome (O): Development of new sensitizations.

Search terms included combinations such as: “allergen immunotherapy” AND new “sensitizations”; “AIT” AND “prevention of allergy” AND “long-term follow--up”; “sublingual immunotherapy” OR “subcutaneous immunotherapy” AND “allergen sensitization”; “allergies prevention” AND “immunotherapy”; “effectiveness of allergen immunotherapy” AND “children” OR “adults”.

Filters were applied to restrict results to English--language publications, with a preference for studies published from 2017 onwards. Nevertheless, older studies were also considered when more recent research was unavailable, as the number of new publications on this specific topic remains limited.

The selection process included several steps: an initial review of titles and abstracts, followed by full-text analysis of eligible articles. Inclusion and exclusion criteria were then applied to determine final eligibility. Only studies that specifically assessed the prevention of new sensitization were included in the final analysis.

From each eligible study, the following data were systematically extracted: type of sensitization in the study population (monosensitized vs polysensitized), mean age of participants, type of AIT administered (SLIT or SCIT), and the presence or absence of a control group. Outcomes related to the development of new sensitizations were recorded, particularly the proportion of patients who developed sensitization to additional allergens during the study period. The quality of the included studies was evaluated using a risk of bias assessment tool. Each study was independently assessed and categorized as having a low, moderate, or high risk of bias based on predefined methodological criteria.

The role of immunotherapy in modulation of immune system

The immune system constantly encounters numerous antigens, particularly through mucosal surfaces, yet it typically maintains a state of controlled unresponsiveness, known as tolerance. This tolerance is vital for the host’s well-being, and when it fails, external antigens or allergens can trigger hypersensitivity reactions, resulting in conditions like allergic rhinitis, asthma, atopic dermatitis, food allergies, or anaphylaxis [8].

Immune and inflammatory cell subsets communicate through cytokines, with key cytokines involved in the allergic response being interleukin 4 (IL-4), IL-13, and IL-5, produced by T helper type 2 cells [8]. These cells and their cytokines influence other cells involved in the allergic response, including eosinophils, mast cells, and basophils, which are the key effector cells in allergic reactions [9]. Th2 cells are also crucial in stimulating B cells to produce allergen-specific IgE [9].

The immune response is triggered when T and B lymphocytes recognize antigenic determinants of allergens, a process regulated by specialized antigen--presenting cells located at mucosal surfaces like the gastrointestinal mucosa, airway epithelium, and dermis [9]. These cells process and present allergenic epitopes to T-helper cells, then in the presence of IL-4, naive T cells activated by antigen-presenting cells differentiate into Th2 cells [10]. IL-4 and IL-13 promote class switching in B cells, resulting in IgE production, which then binds to high-affinity FcεRI receptors on mast cells and basophils, a process known as sensitization [10]. Upon re-exposure to the allergen, these sensitized mast cells and basophils become activated, releasing biogenic mediators such as histamine, proteases, leukotrienes, and cytokines, which are responsible for the symptoms and signs of type 1 hypersensitivity allergic reactions [10].

Natural exposure triggers a quick allergic response with small amounts of allergen, while immunotherapy uses much higher doses, 100 times the annual exposure, and different routes of entry, such as sublingual or subcutaneous, to promote immune tolerance [2].

Allergen-specific immunotherapy works by inducing early desensitization, modulating T- and B-cell responses, altering antibody isotypes, and inhibiting the migration of eosinophils, basophils, and mast cells, along with suppressing mediator release from these cells [11]. One of the mechanisms that AIT alters is a shift from Th2 to Th1 response [11]. Th1 cells produce IFN-γ, which stimulates B cells to generate IgG instead of IgE. Unlike IgE, IgG does not trigger allergic reactions [1]. Regulatory T cells have also been recognized as essential regulators of immune processes in peripheral tolerance to allergens [1]. The shift of allergen-specific effector T cells towards a regulatory phenotype seems to be a crucial factor in developing a healthy immune response to allergens and achieving successful outcomes in allergen-specific immuno-therapy [10]. Treg cells play a significant role in regulating allergen-specific immune responses in several key ways [9,10]. These include the suppression of dendritic cells that promote the generation of effector T cells, inhibition of effector Th1, Th2, and Th17 cells, reduction of allergen-specific IgE levels while promoting IgG4 production, suppression of mast cells, basophils, and eosinophils, and the prevention of effector T cell migration to tissues [9,10]. Inhibition of Th2 cells by Treg cells results in preventing Th2 cells from producing cytokines such as IL-4, IL-5, and IL-13, which are essential for the differentiation, survival, and function of mast cells, basophils, eosinophils, and mucus-producing cells [9]. High-dose allergen administration in immunotherapy boosts endogenous IL-10 production in T cells and antigen--presenting cells, leading to T cell anergy and selective regulation of antigen-specific IgE and IgG4 by B cells,

with a preference for IgG4 [12]. Consequently, elevated IL-10 synthesis in allergic inflammation also suppresses allergy effector cells [12].
Immunotherapy reduces the development of new allergic sensitivities, and long-term follow-up studies show that treatment with standardized allergen extracts provides lasting clinical benefits even after it ends [13].

AIT as a prevention of acquiring new allergies

AIT, commonly used in the treatment of allergic conditions such as allergic rhinitis, asthma, and insect venom allergies, is emerging as a promising strategy not only for alleviating symptoms but also for preventing the development of new allergies [14].
Studies have shown different results depending on the characteristics of the research. The conducted studies were prospective or retrospective observational studies with a long-term observation period, defined as a minimum of three years, encompassing both treatment and follow-up phases. Alternatively, long--term follow-up data from randomized controlled trials of SCIT or SLIT were considered. These studies compared subjects who received AIT to those who did not. The research also included monosensitized or polysensitized patients diagnosed with allergic rhinitis and/or asthma, who had positive allergen-specific skin prick tests and/or elevated serum allergen-specific IgE levels [15].
A low-risk bias double-blind placebo-controlled trial that investigated the development of new sensitizations in adult patients allergic to peach post-AIT and after SLIT found no statistically significant effect of SLIT [16]. Nevertheless, two additional randomized controlled trials, with moderate to high risk of bias, found a significantly reduced incidence of new sensitizations in children and adults with allergies who were treated with SLIT or SCIT, compared to the control groups [17]. Another randomized controlled trial with minimal risk of bias assessed the impact of oral house dust mite AIT in healthy infants at high risk of developing allergic conditions. The findings indicated a significant reduction in sensitization to any common allergen in the intervention group relative to the placebo group [18]. Moreover, a case-control study with a high risk of bias, which compared children of parents who had undergone AIT at least nine months prior to conception with a matched control group, found that the odds of developing any allergic disease were significantly lower in children with at least one allergic parent who had received AIT, in contrast to children with allergic parents who had not undergone the treatment. This suggests that AIT in allergic parents may potentially reduce the risk of allergies in their offspring; however, it warrants further research [19].
The evidence supporting the efficacy of AIT in reducing the likelihood of new allergen sensitizations in allergic monosensitized children is limited in strength and largely based on expert opinion rather than solid evidence. However, the potential preventive effects of AIT on the development of new allergen sensitizations have been endorsed in various reviews and position statements [20]. While the initial data is encouraging, more large-scale, longitudinal clinical trials are necessary to further define the efficacy, safety, and optimal timing of AIT as a preventive strategy [3]. Finally, individual patient factors such as age, the presence of comorbid allergic conditions, and the specific allergens involved must be considered to tailor the most effective preventive approach [21].

Comparison of AIT with other allergy prevention methods

Hydrolyzed formulas, particularly extensively hydrolyzed, have been proposed for infants at high risk of developing allergies. These formulas are broken down proteins that do not trigger an allergic reaction [22]. However, the evidence supporting the effectiveness of this method is not solid. Some studies even suggest no significant allergy prevention effect compared to normal formulas [23]. Nonetheless, hydrolyzed formulas still serve as a crucial preventive strategy by reducing allergen exposure and potentially fostering immune tolerance. Immunotherapy is a therapeutic intervention focused on desensitizing already allergic patients. While studies focusing on hydrolyzed formulas yield mixed results, immunotherapy has well-established efficacy in reducing allergy symptoms and stopping disease progression [24]. In terms of safety, hydrolyzed formulas are generally well-tolerated, while AIT requires monitoring [25]. However, it is still a better option, mainly because of the long-lasting tolerance effect that it causes [26].
Probiotics modulate the gut microbiota, which influences the gut-associated lymphoid tissue, increasing the proportions of Treg cells and changing cytokine profiles to anti-inflammatory patterns. Some studies have shown that recombinant probiotics help shift the immune response from Th2 to Th1 and Treg, indicating their immunomodulatory potential [26]. The disease-modifying effect of immunotherapy stands in contrast to the more variable outcomes seen with probiotics. Some studies have reported that probiotic supplementation can reduce the risk of certain allergic outcomes like eczema and food hypersensitivity in infants; however, those effects are inconsistent [27]. In addition, one study indicated that early-life probiotic supplementation might even increase allergen sensitization in high-risk children, demonstrating that probiotic effects may be strain-dependent and their outcomes not beneficial to some [28]. Administration of probiotics is noninvasive, easily available, and does not require medical monitoring [28]. That makes it a safer option than AIT. However, safety concerns have

been noted in immunocompromised children or in cases where probiotic strains are not carefully selected, with current clinical guidelines remaining cautious about their routine use for allergy prevention [29].

Allergen avoidance is still a primary method of allergy management. It requires necessary and hard work to introduce modifications to the living environment, diet, and behavior to reduce exposure to known allergens. However, for common widespread allergens like grass or pollen, complete avoidance is impractical and near impossible. Studies show that while some lifestyle modifications may reduce exposure, they are often insufficient [30]. In contrast, allergen-specific immunotherapy offers a proactive approach aimed at reprogramming the immune system rather than reducing exposure [31]. While traditional avoidance can ease immediate symptoms, its effects are temporary and do not modify the natural history of a disease [32]. Studies prove that many patients continue to experience persistent symptoms and are at constant risk for severe reactions despite implementing avoidance measures. In contrast, AIT has been shown to provide long-term benefits. Immunotherapy not only alleviates symptoms but also improves overall allergen tolerance and the progression of the disease [26]. Avoidance strategies are generally considered safe. However, their practicality is limited by the lack of ways to eliminate exposure to allergens completely, particularly in the context of outdoor allergens. In addition, restricting certain foods may lead to nutritional deficiencies and raise burdens on the whole family of the patient, as caregivers must carefully plan diets and remain in a constant state of alert about hidden allergens. Immunotherapy, on the other hand, is more invasive and requires professional monitoring due to the risks of local and systemic allergic reactions [33].

Table I presents a comparative overview of various preventive strategies for allergic diseases in children. It summarizes key aspects of each method, including their mechanism of action, effectiveness, safety, and practical considerations such as availability and long--term benefits.

Table I. Comparison of preventive strategies for allergic diseases

Method	Mechanism of action	Effectiveness	Safety	Practicality and long-term benefits
Hydrolyzed formulas	Reduces allergen exposure by using broken-down proteins to prevent allergic reactions	Mixed evidence; some studies show no significant prevention effect compared to normal formulas	Generally well-tolerated	Useful for high-risk infants but lacks long-lasting tolerance effects
Probiotics	Modulates gut microbiota, promotes Treg cells, and shifts immune response from Th2 to Th1/Treg	Inconsistent results; may reduce eczema but can increase sensitization in some cases (strain-dependent)	Noninvasive, no monitoring needed, but caution in immunocompromised children	Easily available but not universally beneficial; clinical guidelines remain cautious
Allergen avoidance	Reduces exposure to known allergens through dietary and environmental changes	Limited effectiveness, especially for widespread allergens (e.g., pollen)	Generally safe but can lead to nutritional deficiencies and lifestyle burdens	Temporary symptom relief; impractical for complete avoidance; no disease--modifying effect
Allergen immunotherapy (AIT)	Desensitizes the immune system, promotes long-term tolerance	Well-established efficacy in reducing symptoms and preventing disease progression	Requires monitoring due to risk of allergic reactions	Long-lasting benefits, modifies disease course, but more invasive than other methods

Conclusions

Allergen immunotherapy provides a novel approach to allergy prevention by reshaping the immune response, moving it away from a Th2-dominated pattern toward a more tolerant, regulatory state. Studies show that AIT can lower the risk of new sensitizations, especially for respiratory allergens like pollen or insect venom, though results can vary. For example, mite immunotherapy in infants reduced general sensitization but not mite-specific IgE, and SLIT for peach allergy had a minimal preventive effect. That is why AIT needs to be personalized depending on the allergen type, age, and immune status of a patient.

When compared to traditional methods like hydrolyzed formulas or probiotics, the difference between them is that AIT offers benefits even after treatment ends. AIT is also better than avoidance strategies as it promotes adaptation of the immune system, whereas avoidance strategies do not. However, its multi-year commitment and need for medical supervision are factors that discourage many patients from undergoing such treatment. Some data also suggest AIT-treated parents might pass protective benefits to children, although the mechanisms of this are unclear.

Studies suggest that AIT might be associated with a reduced risk of developing new sensitizations, particularly when the duration of treatment exceeds

three years. This preventative effect appears to be more pronounced in pediatric populations and in monosensitized individuals. Evidence also indicates that AIT may alter the natural course of allergic disease and exert a prophylactic effect. However, these findings must be interpreted with caution due to limitations inherent in the existing body of research, including variability in study methodologies, heterogeneous patient populations, and a lack of standardized outcome measures. Consequently, further well-designed, longitudinal studies are warranted to definitively determine the efficacy of AIT in preventing the development of sensitization in individuals with pre-existing allergic conditions. Future research must focus on large trials, standardized protocols, and biomarker-based personalization – all while balancing cost, access, and patient adherence.

Authors' contribution

Study design – A. Zalewska, W. Hariasz

Manuscript preparation – A. Zalewska, M. Drobik, M. Michałek, M. Kozieł, W. Hariasz, K. Gądek, A. Lichodij

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