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MECHANISMS AND CLINICAL PERSPECTIVES OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Abstract. Introduction: Allergic rhinitis (AR) is a prevalent condition in Kazakhstan, characterized by high sensitization to weed pollens, particularly Artemisia, with sensitization levels significantly exceeding those observed in Europe. AR often leads to complications such as bronchial asthma (BA) and other respiratory conditions. The "unified airways" concept emphasizes the interconnected nature of upper and lower airway inflammation, with ASIT showing promise in mitigating these effects.
Materials and Methods: A systematic review included 51 articles published between 2013 and 2024, selected from databases such as PubMed and Scopus. Studies focused on ASIT in AR and the role of vitamin D. Inclusion criteria required full-text original research and systematic reviews in Russian and English, specifically addressing allergen-specific immunotherapy.
Results and Discussion: ASIT promotes immunological tolerance through mechanisms such as suppression of Th2 activity, increased IgG4 production, and reduced effector cell activation. Vitamin D, particularly 25(OH)D, plays a pivotal immunomodulatory role, supporting Treg and Breg cell function, and mitigating allergic inflammation. Clinical trials demonstrate that vitamin D supplementation enhances ASIT outcomes, especially in pediatric patients.
Conclusion: Integrating cholecalciferol into ASIT protocols enhances efficacy and safety by addressing vitamin D deficiency, a factor linked to more severe allergic diseases. This highlights the importance of personalized treatment strategies combining ASIT with vitamin D supplementation for optimal outcomes.
Key words: allergic rhinitis, allergen-specific immunotherapy, vitamin D, tolerance.

Introduction

Allergic rhinitis (AR) in the Republic of Kazakhstan (RK) is characterized by a distinct pattern of sensitization to causative allergens, with a trend toward increased sensitization to weed pollens, particularly Artemisia (wormwood) [1,2]. The intensity of sensitization to these allergens exceeds by a million times the levels recorded in Central Europe and the European part of the Russian Federation [3,4]. One of the most common pollen allergens in Europe and North America is Timothy grass [5]. Other studies indicate that birch pollen is a frequent cause of pollen sensitization[6].Sensitization to aeroallergens affects at least 40% of the population in Europe, the USA, Australia, and New Zealand[7].

In the absence of timely treatment, AR often leads to the development of associated conditions such as allergic conjunctivitis, bronchial asthma (BA), chronic sinusitis, Eustachian tube dysfunction, nasal polyposis, serous otitis media, and other respiratory diseases[8,9]. The most common complication of AR is BA, affecting 10–40% of the population[10]. A history of AR in children increases the risk of developing bronchial asthma threefold by the age of 20–40 years and fourfold by the age of 12–20 years[11]. The concept of "unified airways" suggests that inflammation in the upper airways also impacts the lower airways [12,13]. Research has demonstrated that treating the inflammatory process in the nasal mucosa has a concurrent therapeutic effect on inflammation in the lower airways, leading to a reduction in asthma symptom severity[14].

Research Objective-To investigate the role of allergen-specific immunotherapy (ASIT) in allergic rhinitis (AR) and the potential role of vitamin D in ASIT.

Materials and Methods

Russian- and English-language articles were analyzed using search engines such as CyberLeninka, PubMed, Scopus, Google Scholar, and e-Library. Searches were conducted with relevant keywords and medical subject headings (MeSH terms) among materials published from 2013 to 2024. A total of 51 articles focusing on ASIT in AR and the role of vitamin D in ASIT were included in the review. The initial search yielded 543 articles, of which 51 met the inclusion criteria and were incorporated into this analysis.

The inclusion criteria for articles retrieved from Russian-language search engines required full-text original studies, systematic reviews, or reports using the following keywords: allergen-specific immunotherapy, allergic rhinitis.

Results and Discussion

Current Perspectives on the Mechanism of Allergen-Specific Immunotherapy

Allergen-specific immunotherapy (ASIT) is a disease-modifying treatment with a high level of evidence (Ia) and a grade A recommendation [15]. The clinical efficacy of ASIT is demonstrated by the reduction in the severity of allergic rhinitis (AR) symptoms, decreased need for anti-allergic medications, prevention of polysensitization, and reduction in the risk of developing bronchial asthma (BA) in AR patients, ultimately improving their quality of life. The core of the method involves the systematic administration of gradually increasing doses of the allergen responsible for the clinical manifestations of the disease. This approach induces specific hyposensitization, promoting the development of immunological tolerance to the causative allergen [16].

Globally, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the most widely used ASIT methods. SCIT is administered by an allergist exclusively in a specialized medical setting[17]. Following each injection, the patient must remain under medical supervision for at least 30 minutes due to the potential risk of systemic adverse reactions [18].

Recently, SLIT has gained popularity due to its convenience and favorable safety profile[19]. The first dose of SLIT is administered under the supervision of a physician, after which patients follow a prescribed regimen independently, with periodic follow-up visits. According to international guidelines and clinical recommendations, ASIT should be conducted for 3–5 years to achieve sustained results, although initial therapeutic effects are typically observed within the first year [20].

ASIT promotes the development of immunological tolerance through several mechanisms:

1. Induction of Early Desensitization of Mast Cells and Basophils;

2. Induction of Allergen-Specific T-Regulatory (Treg) and B-Regulatory (Breg) Cells: ASIT promotes the development of Treg and Breg cells, which suppress allergen-specific effector T-cell subpopulations. These regulatory cells secrete IL-10 and TGF-β, key mediators of immune tolerance[21];

3. Regulation of Allergen-Specific Immunoglobulin Levels: ASIT reduces the concentration of specific IgE (sIgE) while enhancing the production of specific IgG4 (sIgG4) and IgA (sIgA). This shift supports the suppression of allergic inflammation and the establishment of tolerance [22];

*4. Reduction in Effector Cell Activity in Target Organ Mucosa:*ASIT decreases the number and activity of effector cells, such as mast cells, basophils, and eosinophils, in the mucosa of target organs. It also reduces basophil activity in peripheral blood, contributing to a reduced allergic response[23].

Understanding these mechanisms underlying the induction and persistence of immunological tolerance is key to developing new, more effective strategies for individualized therapy, as well as to identify prognostic biomarkers of clinical response [24].

Induction of Early Desensitization

ASIT suppresses the early phase of allergic reactions by selectively modulating histamine receptors, which decreases the sensitivity of mast cells, eosinophils, and basophils to degranulation despite elevated levels of specific IgE (sIgE). Studies on the early phase of tolerance induction show that within the first six hours, histamine receptor regulation suppresses basophil activation and mediator release. Histamine receptors also exhibit strong immunoregulatory activity on T cells, dendritic cells, and basophils[25] [26].

T-Regulatory (Treg) and B-Regulatory (Breg) Cells

Treg and Breg cells, which produce interleukin-10 (IL-10), are key players in the establishment of immunological tolerance. These cells inhibit type 2 helper T-cell (Th2)-mediated allergic responses through IL-10 secretion, reducing inflammation and promoting tolerance. Treg cells play a central role in the success of ASIT, with a significant correlation observed between symptom improvement and Treg cell counts during therapy. Their immunosuppressive

functions include direct interactions with Th2 cells and inhibition of IL-4, IL-5, IL-9, and IL-13 production. Additionally, Treg cells secrete IL-10 and transforming growth factor-beta (TGF-β), which shift the immune response from IgE to IgG4 and IgA, stabilizing early desensitization effects and sustaining them for weeks after therapy initiation [27][28][29][30].

Breg lymphocytes are activated earlier during the allergic reaction and play a critical role in recruiting Treg cells into the immune response. Similar to Treg cells, Breg lymphocytes are significant sources of IL-10 and TGF-β, which suppress Th2 proliferation and exert their effects through direct cell-to-cell interactions. These mechanisms enhance the production of IgA, IgG1, and particularly IgG4, whose concentration increases by 10–100 times during ASIT.

Breg lymphocytes maintain the balance necessary for the development of immunological tolerance and regulate excessive inflammatory responses through IL-10 secretion. IL-10, in turn, inhibits pro-inflammatory cytokines and supports the differentiation of Treg cells, reinforcing the regulatory network essential for effective and sustained tolerance [31].

Effect on IgE and IgG4 Production

A key mechanism underlying the development of immunological tolerance during ASIT is the shift in immune response from the production of specific IgE (sIgE) to the production of specific IgG4 (sIgG4) [32]. Several studies confirm that an increase in serum sIgG4 levels during both the early and late phases of therapy is associated with clinical improvement and plays a critical role in the development and maintenance of the long-term effects of ASIT [33].

sIgG4 prevents the binding of IgE to mast cells and basophils, thereby blocking immediate allergic inflammation [34]. Furthermore, sIgG4 inhibits IgE-mediated allergen presentation to T cells, reducing allergen-specific T-cell activation and the production of inflammatory cytokines. This results in the suppression of T-cell-mediated allergic inflammation and likely limits eosinophil activation [35].

Late Desensitization

Late desensitization develops over several months from the initiation of therapy [36]. The therapeutic effects of ASIT include a reduction in the number of mast cells and eosinophils in tissues and an increased activation threshold for eosinophils and T cells [37]. This leads to decreased nasal, bronchial, and skin reactivity to allergen provocation, which underpins the efficacy of the therapy [38]. Successful ASIT raises the threshold concentration of allergens required to induce immediate reactions or late-phase allergic inflammation in the target organ. Additionally, ASIT suppresses both allergen-specific and non-specific tissue hypersensitivity.

The primary mediators of immunological tolerance are **interleukin-10 (IL-10)**and**transforming growth factor-beta (TGF-β).** IL-10 is produced by nearly all leukocyte types, including Treg, Breg, monocytes, and, to a lesser extent, macrophages, natural killer cells, and dendritic cells [39].The induction of immunological tolerance to allergens during ASIT involves multiple mechanisms, including the suppression of Th2 activity, inhibition of IL-4 and IL-5 production, and initiation of Treg cell differentiation. It also promotes a switch in plasma cell synthesis from IgE to IgG4, thereby reducing sIgE levels, and inhibits the expression of IgE receptors on mast cells. Notably, studies have demonstrated a correlation between elevated IgG4 levels and IL-10 concentrations in the blood, highlighting the role of IL-10 in mediating these effects.[40].

TGF-β, predominantly synthesized by Treg cells, plays a crucial role in establishing immunological tolerance during ASIT. Although TGF-βis also produced by eosinophils, Breg, epithelial cells, fibroblasts, and macrophages, Treg cells remain its primary source. The main effect of TGF-β is mediated by inhibiting the proliferation and differentiation of B cells, which enhances IgA and IgG4 secretion while suppressing Th2 activity [41]. IL-10 and TGF-β inhibit the recruitment of effector cells (eosinophils and basophils), thereby limiting local inflammatory responses. A key property of their tolerogenic activity is their ability to suppress the expression of major histocompatibility complex (MHC) class II molecules and co-stimulatory molecules on antigen-presenting cells (APCs), effectively blocking the further development of immune responses to allergens [42].

The Role of Cholecalciferol in Allergen-Specific Immunotherapy

Vitamin D has been established as a participant in allergic processes and is regarded as an immunomodulator that influences dendritic cells (DCs), macrophages, T cells, and B cells[43]. Activated B lymphocytes, T lymphocytes, and myeloid antigen-presenting cells (APCs) can synthesize biologically active calcitriol from 25-hydroxyvitamin D (25(OH)D), an inactive precursor. Receptors for 25(OH)D have been identified on blood monocytes, as well as on activated T and B lymphocytes. In this context, T lymphocytes become direct targets for the active form of vitamin D, which exerts regulatory effects on circulating chemokines and cytokines [44].

25(OH)D suppresses the differentiation, maturation, and immunostimulatory activity of DCs by

blocking the expression of MHC class II molecules. Physiological levels of 25(OH)D support tolerogenic DCs that produce IL-10 [45]. Moreover, 25(OH)D helps maintain the balance between Th1 and Th2 cells. Some studies indicate that 25(OH)D deficiency may result in increased Th2 activity, decreased Treg activity, and reduced IL-10 production. Adequate 25(OH)D levels in the blood contribute to the suppression of IgE production and enhanced IL-10 secretion by B lymphocytes. The immunomodulatory effects of 25(OH)D may be dose-dependent: standard doses inhibit Th1 and Th2 cytokine production, while high doses might amplify the Th2 response [46].

Over the past decade, there has been an increase in research exploring the relationship between 25-hydroxyvitamin D (25(OH)D) levels in the blood and the development and severity of allergic diseases. Studies have demonstrated a correlation between serum 25(OH)D concentration and the condition of patients with allergic rhinitis (AR). It has been established that the prevalence of severe 25(OH)D deficiency is significantly higher among AR patients compared to the general population [47,48]. Research suggests that 25(OH)D deficiency may lead to eosinophil activation and the release of elevated levels of eosinophilic cationic protein, which, in turn, exacerbates nasal mucosal inflammation in AR patients [49].

Several clinical trials have demonstrated that the addition of cholecalciferol plays an important role in the prevention of allergic rhinitis (AR), bronchial asthma (BA), and other allergic diseases. A study evaluating the efficacy of cholecalciferol as an adjuvant combined with sublingual immunotherapy (SLIT) for pollen and dust mite allergies in children showed high safety and efficacy. Patients who received daily oral cholecalciferol for five months in combination with SLIT exhibited significant symptom improvement compared to those undergoing SLIT alone [50].

Current evidence supports the critical role of vitamin D in the pathogenesis of allergies and highlights the impact of its deficiency on the increased risk of developing various allergic diseases, their more severe progression, and reduced treatment efficacy [51]. This underscores the need for a detailed examination of 25(OH)D deficiency and insufficiency in allergic pathology and the broader adoption of comprehensive approaches that incorporate cholecalciferol into ASIT treatment protocols to achieve optimal therapeutic outcomes.

Conclusion

Allergen-specific immunotherapy (ASIT) remains a cornerstone in the management of allergic rhinitis (AR) and other allergic conditions, offering a disease-modifying approach that promotes long-term immunological tolerance. The addition of vitamin D, particularly cholecalciferol, has shown promise in enhancing the efficacy and safety of ASIT by modulating immune responses and addressing deficiencies that may exacerbate allergic diseases. Current evidence underscores the importance of maintaining adequate 25-hydroxyvitamin D (25(OH)D) levels for improving therapeutic outcomes and reducing disease severity. Further research is warranted to refine treatment protocols that integrate vitamin D supplementation, paving the way for more effective and personalized strategies in allergy management.

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