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Поиск предиктивных биомаркеров эффективности аллергенспецифической иммунотерапии на основе современных представлений о механизмах её действия

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АННОТАЦИЯ

Аллергенспецифическая иммунотерапия является основным патогенетически обоснованным методом лечения аллергических заболеваний, действие которого не только приводит к уменьшению выраженности клинических симптомов, но и оказывает болезнь-модифицирующий эффект, препятствуя прогрессированию заболевания, развитию бронхиальной астмы и расширению спектра сенсибилизации.

Толерантность, формируемая в процессе аллергенспецифической иммунотерапии, опосредована сложным взаимодействием между различными клетками врождённого и адаптивного иммунитета. Несмотря на то, что к настоящему времени описаны основные механизмы действия аллергенспецифической иммунотерапии, с каждым годом представление об этих процессах становится всё более детализированным не только на клеточном, но и молекулярном и эпигенетическом уровнях. В свою очередь, глубокое понимание механизмов, лежащих в основе формирования и сохранения толерантности к аллергенам при проведении аллергенспецифической иммунотерапии, поможет в выявлении предиктивных биомаркеров эффективности, использование которых могло бы оптимизировать отбор пациентов для проведения аллергенспецифической иммунотерапии, предсказывая ответ пациента на терапию.

В настоящем обзоре изложены актуальные представления о механизмах действия аллергенспецифической иммунотерапии на различные звенья аллергического процесса; описаны предполагаемые предиктивные биомаркеры эффективности данного терапевтического метода с учётом перспективных направлений исследований в этой области.

Ключевые слова: аллергенспецифическая иммунотерапия; АСИТ; механизмы аллергенспецифической иммунотерапии; предиктивные биомаркеры; биомаркеры эффективности.

Как цитировать

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Searching for predictive biomarkers of allergen-specific immunotherapy efficacy based on modern concepts of its mechanisms

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ABSTRACT

Allergen-specific immunotherapy is the primary pathogenetically substantiated method for treating allergic diseases.
This treatment decreases the severity of clinical symptoms, has disease-modifying effects, and prevents disease progression, asthma development, and the spread of sensitization. A complex interaction between various cells of innate and adaptive immunity mediates immunological tolerance driven by allergen-specific immunotherapy. Although the primary mechanisms of allergen-specific immunotherapy have been described to date, the understanding of these processes becomes more detailed at the cellular, molecular, and epigenetic levels each year. As a result, deep insights into the mechanisms underlying the development and maintenance of tolerance to allergens during allergen-specific immunotherapy can help reveal the predictive biomarkers of efficacy. These biomarkers can streamline the selection of patients via the identification of responders to allergen-specific immunotherapy.
This review presents the current concepts of allergen-specific immunotherapy mechanisms at various stages of the allergic process. Furthermore, the predictive biomarkers of the efficacy are described, with consideration of promising directions of research in this area.

Keywords: allergen-specific immunotherapy; allergen immunotherapy; AIT; mechanisms of allergen immunotherapy; predictive biomarkers; efficacy biomarkers.

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INTRODUCTION

Allergen immunotherapy (AIT) is a unique method of treatment of allergic diseases based on the induction of clinical tolerance to allergens by introducing repeated doses of allergens at regular intervals [1]. Currently, AIT is the only pathogenetically substantiated treatment of IgE-mediated diseases. AIT reduces the severity of clinical symptoms and the patient's need for symptomatic therapy and changes the disease course, preventing its aggravation, asthma onset, and spread of sensitization to allergens. A successful AIT leads to a decrease in symptom severity or complete absence of symptoms, can be chronic, and persist for several years after therapy, which is currently not characteristic of any other treatments for allergic diseases [2].

The use of AIT as a treatment of allergic diseases dates back more than 100 years; however, the exact mechanisms of this method are still being investigated [3]. The cellular and molecular mechanisms underlying the induction of clinical tolerance during AIT have been studied over the past decades. These mechanisms are mediated by complex interactions between cells of innate and adaptive immunity through the spectrum of cytokines. Although the main mechanisms of AIT have been described, these processes become increasingly understood in more details because of advances in biomedical science. Owing to differences in the responses of patients to AIT (i.e., responders and nonresponders), the current scientific trend is the search for predictive biomarkers of clinical response. A deep understanding of the mechanisms underlying the induction and maintenance of tolerance to allergens during AIT will help in identifying these biomarkers and developing new immunotherapy strategies [4].

This review analyzes current studies of the mechanisms of AIT for inhaled allergens. Possible predictive biomarkers of AIT efficacy and promising research directions in this area are also described.

MECHANISMS OF AIT

AIT has comprehensive effects on the immune response, which affects both the early and late phases of allergic reactions. This effect is accomplished through the induction of tolerance to the allergen, realized by the influence on various stages of the allergic process [3].

Mast cells and basophils

Mast cells and basophils play key roles in the pathogenesis of the effector phase of type I hypersensitivity reactions. During AIT, their desensitization occurs within a short time from treatment initiation, which is manifested by a decrease in the sensitivity of mast cells and basophils to allergens, despite the high levels of allergen-specific IgE at treatment initiation. At later AIT stages, tissue infiltration of mast cells and basophils and the intensity of their degranulation and release of mediators decreased [5]. The desensitization of mast cells and basophils is achieved by increasing the production of allergen-specific IgG4 and expression of low-affinity IgG receptors (FcγRIIa and FcγRIIb) on these cells. This IgG-mediated inhibition reduces the secretion of proinflammatory cytokines in mast cells and basophils [6] and the activation of type 2 histamine receptors, which is more rapid and has an inhibitory effect on FcεRI-mediated activation and degranulation of basophils [7].

Dendritic cells (DCs)

DCs are mature antigen-presenting cells that can induce and maintain both allergic inflammation and allergen tolerance. DCs play an important role in the effect of AIT. AIT causes an increase in the number of plasmacitoid DCs, decrease in the number of conventional DCs involved in Th2-immune response in patients with allergies, and switching the DC phenotype (DCregs). DCregs produce interleukin (IL-10) and induce the formation of a T-regulatory cell pool [5, 8].

Studies have demonstrated that AIT with allergoid mannan conjugates induced the production of tolerogenic DCs, producing IL-10, and reprogrammed monocytes and macrophages into tolerogenic phenotypes [9–12]. In the genetic study of cells, patients also showed high levels of mRNA expression for stabilin and C1q, which is a characteristic feature of DCregs, detected only among those patients with allergies and receiving AIT [13]. IL-27 is another important cytokine produced by DC, which is associated with the inhibition of the peripheral mononuclear cell proliferation, induced by allergens, reduces IL-4 and IL-5 production, and increases the production of IL-10 and interferon (IFN)-γ [14].

T-lymphocytes

T-lymphocytes play a significant role in the AIT mechanism. A decrease in the number of CD4+ Th2-cells and local T-cells in the nasal mucosa producing IL-4 is a result of AIT [15]. Current research methods led to the identification of the phenotypes of peripheral circulating allergen-specific T-cells; thus, the key surface markers of T-cells, such as CD27, CRTH2, CD161, and CCR4, could be specified. Specifically, patients with allergies had high levels of CRTH2 and CCR4 and low levels of CD27, whereas in patients without allergies had T-cells with low levels of CRTH2 and CCR4 expression and a high level of CD27. Patients who received AIT with birch pollen allergens had decreased number of CD27-Th2 cells [16–19]. This finding was also confirmed in patients who received both subcutaneous and sublingual AIT as part of the GRASS study. Moreover, these changes were accompanied by a decrease in the level of Th2 cytokines, including IL-4, IL-5, and IL-13, in the nasal fluid after the nasal allergen provocation test [20, 21].

Regulatory T-cells (Tregs)

The balance between regulatory and effector T-cells affects the induction and maintenance of peripheral tolerance to allergens. Peripheral T-cell tolerance is characterized

by an increase in the number of Tregs induced by AIT and the polarization of the immune response toward Th1 [22]. The suppression of various effector cells by Tregs is a key mechanism for establishing cell-mediated tolerance. Among allergen-specific Tregs, thymic and inducible Tregs (iTregs) are distinguished. iTregs include FOXP3-expressing iTregs, IL-10-secreting Tr1, and transforming growth factor-β (TGF-β)-producing Th3 cells [23, 24]. During AIT, Tregs suppress the function of effector cells and promote the production of blocking antibodies by B-lymphocytes [25].

AIT with domestic mite allergens increased the number of allergen-specific Tregs and decreased the level of transmembrane immunoglobulin-like protein ILT3, which has a suppressive effect on Tregs in an ex vivo study [26]. Moreover, AIT modifies the epigenetic mechanisms, contributing to the induction of tolerance to allergens. DNA methylation is the most studied epigenetic factor in AIT [27]. In AIT, cytosine bases in CpG dinucleotide can gain a methyl group using a DNA methyltransferase enzyme. The methylation of the promoter areas of genes prevents the binding of transcription factors to these sites, which helps inhibit gene expression. Gene hypomethylation helps enhance transcription from these sites [28]. During AIT, the promoter areas of the *FOXP3* gene become hypomethylated, which enhances the expression of this gene and contributes to the formation of a Treg pool in certain studies [29, 30]. However, after AIT, the promoter areas of the *IL4* gene became hypermethylated, which reduces the expression of the proinflammatory cytokine IL-4 [31].

Following AIT, the number of IL-10-producing Tregs increases. Moreover, IL-35-induced Tregs have been identified as a separate iTreg group that can reduce Th2 inflammation, T-cell proliferation, and cytokine production by ILC2 cells [32, 33]. Recent studies have also demonstrated that successful subcutaneous AIT increases the levels of IL-35- and IL-35-induced Tregs in the peripheral blood [5]. All these studies have confirmed the important role of allergen-specific Tregs in the development of tolerance during successful AIT.

Allergen-specific antibodies

The production of immunoregulatory cytokines, such as IL-10 and TGF-β, by the aforementioned cells leads to the suppression of Th2-immune response and a shift toward the induction of allergen-specific antibodies IgA and IgG4 [22, 34, 35]. Non-IgE allergen-specific antibodies compete with IgE for the allergens, which inhibits the IgE-mediated cross-binding of FcεRI on basophils and mast cells at the cellular level, reducing the activation of mast cells and basophils [36].

Studies have demonstrated that AIT increased the production of allergen-specific IgG4 antibodies. Moreover, specific IgG4 contributed to the formation of an anti-allergic immune response [37]. Studies have described several mechanisms characterizing the regulation of allergic inflammation by IgG4 [36]. The bispheric nature of IgG4 antibody, which has two antigen-binding sites, contributes to one of these mechanisms. Fab-arm exchange results in the formation of functionally monovalent antibodies, which prevents the formation of immune complexes [38]. In addition, IgG4 has a low affinity to Fcγ receptors, does not bind to the complement components, and competes with IgE, blocking its binding with allergens [36]. Similar to IgG4, the IgE-blocking effect is also shown in IgG2. Recent studies have shown that IgG2 and IgG4 production is induced in patients receiving sublingual immunotherapy with grass pollen allergens [39]. In addition, a study reported an increase in the levels of allergen-specific IgD caused by dust mite allergy in patients with asthma who received AIT with a causal allergen [40].

Regulatory B cells

A recent study showed that B-cells producing specific antibodies can also regulate immune reactions using alternative mechanisms [41]. Regulatory B cells (Bregs) play a crucial role in the production of anti-inflammatory cytokines such as IL-10, IL-35, and TGF-β and expression of immunosuppressive receptors, including B-cell receptor, PDL-1, CD39, CD73, CD80/CD86, CD40, inducible T-cell costimulator ligand (ICOS-L), and aryl hydrocarbon receptor [42]. Bregs can be induced by various factors, including the effects of proinflammatory cytokines, such as IL-6, IL-1b, and IFN-α, and microbial agents [43].

During AIT with honeybee venom allergen, the number of IL-10-producing Bregs, which is specific to phospholipase A2 of this allergen and can produce IgG4, increases [44]. The number of IL-10+Bregs increased in patients with allergies who received AIT or were exposed to the natural effects of allergens [45]. In addition, a significant increase was observed in the number Der p1-specific B cells, plasmoblasts, and IL-10+IL-1RA+Bregs in patients with dust mite allergy receiving AIT [26]. Thus, Bregs play one of the key roles in achieving immune tolerance during AIT.

Innate lymphoid cells (ILCs)

ILCs are a relatively recently described type of innate immunity. These cells are classified into two main groups: cytotoxic and noncytotoxic (helper) ILCs. Cytotoxic ILCs include NK cells, whereas noncytotoxic ILCs are categorized into three phenotypes: ILC1, ILC2, and ILC3. These three cell groups functionally resemble Th1, Th2, and Th17, respectively. ILC2 produces IL-4, IL-5, and IL-13 and plays an important role in the pathogenesis of allergic reactions [46, 47]. After AIT with grass pollen, a pronounced inhibition of the seasonal increase in the number ILC2 was noted [48].

BIOMARKERS OF THE CLINICAL EFFICACY OF AIT

Currently, clinical indicators demonstrating the reduction in symptom severity and the need for medications during natural exposure to allergens are the gold standard for

assessing AIT efficacy [4]. Validated scales and questionnaires, such as the combined symptom and medication score, visual analog scale [49], asthma control questionnaires (asthma control test and asthma control questionnaire-6), quality-of-life questionnaires (rhinoconjunctivitis quality of life questionnaire and asthma quality of life questionnaire) [50], can be used for the assessment. However, these methods are subjective and can only be used for a retrospective assessment of therapy efficacy. Thus, the use of predictive biomarkers of AIT efficacy could optimize patient selection for AIT, predicting their response to therapy; thus, the search for such biomarkers continues.

Biomarkers are quantitatively measurable indicators that allow the clinical practitioner to diagnose and assess disease severity and predict and monitor the clinical response to therapy [51]. Currently, candidate biomarkers of the clinical efficacy of AIT are characterized below.

IgE

When choosing a medication for AIT, the level of specific IgE (sIgE) to the causative allergen in the blood serum is one of the important indicators of allergy diagnostics [52]. In most cases, assessing the sIgE level to the whole allergen extract to make a diagnosis and select an allergen for AIT is sufficient. However, in difficult diagnostic situations, molecular allergodiagnostic methods of determining sIgE to allergen components can be used [53]. When AIT is performed both subcutaneously [54] and sublingually [55], the sIgE level is increased at the initial stages of treatment. Subsequently, sIgE levels gradually decreased [56], and the seasonal increase in sIgE became less prominent, compared with the years before treatment. However, no clear correlation between the decrease in sIgE and the clinical response has been found [57, 58]. In several studies, the change in the sIgE-to-total IgE ratio correlates with the clinical effect of AIT after therapy [59, 60]; however, these results were not reproduced in a randomized trial [61].

Considering the ease of measuring IgE, this biomarker is currently considered one of the candidates for assessing AIT efficacy; however, studies must validate this method.

IgG and IgA

Levels of IgG and IgA can be also monitored during AIT using simple laboratory methods. Studies have demonstrated an increase in allergen-specific IgG1 and IgG4 levels up to a hundredfold during AIT compared with the initial levels; however, no correlation with clinical response to therapy has been found [62–64]. Thus, the assessment of the increase in serum IgG and IgG4 levels was suggested to monitor patients' adherence to treatment because the progressive increase in these indicators reflects high allergen exposure [65]. A decrease in the sIgE-to-sIgG4 ratio during subcutaneous AIT was associated with a reduced risk of the development of local reactions; however, the results obtained have not been reproduced in other studies [4].

The IgG-mediated inhibition of IgE detected by flow cytometry (flow cytometry-based assay, i.e., IgE facilitated allergen binding [FAB]) is another promising biomarker [66]. This assay determines the ability of the serum of patients receiving AIT to inhibit FcεRII-mediated binding of allergen–IgE complexes to B-lymphocytes because of allergen-specific IgG, IgA, and IgD blocking B-cell antigen presentation to T-helper cells. Thus, the enzyme-linked immunosorbent-FAB (ELIFAB) assay, a simpler laboratory method, can be employed to monitor the same biomarker [67]. These methods characterize the functional activity of serum, and according to a few studies, a moderate correlation was found between the clinical effect of AIT and these biomarkers [54, 67].

The levels of local sIgG and sIgA in secretions must be assessed because they characterize the change in the direction of the immune response in target organs after AIT. Certain studies have demonstrated that AIT leads to an increase in the level of sIgG (including sIgG4) in nasal secretions and saliva, which was also associated with the clinical effect [20, 68]. Unlike subcutaneous AIT, sublingual AIT induced sIgA production by the cells of the nasal mucosa [34].

The study of these local biomarkers is promising because of the availability of laboratory methods of enzyme immunoassay and direct manifestation of the immune response in the main target organ in respiratory allergies.

Basophil activation

Basophil activation is an important indicator. It can be assessed using flow cytometry with surface markers CD63 and CD203c [69]. CD63 is a marker of basophil degranulation. CD203c is a specific marker of IL-3-mediated basophil activation. Diamine oxidase, which stains intracellularly with phycoerythrin, can be examined to investigate the activation of basophils. Diamine oxidase binds strongly to its substrate histamine in cells; thus, the stimulation of basophils, and their degranulation upon interacting with the allergen decreased intracellular diamine oxidase in proportion to histamine release.

Studies have demonstrated a relationship between the decrease in basophil activation and the development of a stable clinical effect of AIT [70, 71].

Cytokines and chemokines

Given that AIT leads to the polarization of the immune response, changes in the levels of Th2 cytokines (IL-4, IL-13, and IL-9), pro-inflammatory cytokines (IL-17, eotaxin, and TNF-α), Th1 cytokines (IFN-γ and IL-12) and regulatory cytokines (IL-10 and TGF-b) can be assessed during AIT to evaluate its efficacy [25]. However, studies to date have shown varying results. Some studies have shown an increase in gene expression levels and serum levels of Th1 cytokines [62, 72–76], whereas others have shown no such changes [77, 78]. Likewise, no clear relationship was found between changes in cytokines and clinical outcomes. Studies have

shown an increase in chemokine CCR4 [79] and apolipoprotein A-IV [80] and changes in complement components [81, 82], eotaxin [79, 83], and leptin [84]. However, the changes in these substances did not demonstrate a clear correlation with the clinical effect of AIT.

Although no relationship between the changes in serum cytokines and the clinical effect of AIT has been identified, the assessment of the tissue cytokine profile is a more promising line of research [83, 85]. A study demonstrated a statistically significant decrease in Th2 cytokines and chemokines in nasal secretion after the allergen provocation test in patients receiving AIT [83].

Metabolic biomarkers

A prospective study examined the changes in serum metabolome during sublingual AIT with house dust mite allergens. In patients with high treatment efficacy, a change in the levels of metabolites such as lactic acid, ornithine, linoleic acid, creatinine, arachidonic acid, and sphingosine was demonstrated 3 years after therapy initiation [86]. In another metabolomic study, exchange reactions of arachidonic and linoleic acids and related changes in the levels of metabolites 13-HODE, 9-HPODE, 5(S)-HETE, 8S(S)-HETE, 11(S)-HETE, 15(S)-HETE, and 11-hydro TXB2 also correlated with the efficacy of subcutaneous AIT with house dust mite allergens [87].

Other cellular and molecular biomarkers

Phenotypic markers of T-cells (Th2, Treg, Tfh/Tfr, and Th1-cells), DCs, and Bregs, detected by flow cytometry, can be used as cellular biomarkers of the clinical efficacy of AIT. Studies have shown a modification of surface markers of these cells during AIT and a correlation between these modifications and the clinical effect. However, no significant results were obtained in studies using these biomarkers as predictors of clinical response and thus identifying responders to therapy [62, 83, 88]. In addition, when assessing a spectrum of markers with flow cytometry, many sample preparation conditions must be achieved for the reliability and reproducibility of the results.

Depending on the spectrum of molecular markers expressed by DCs, their ability to induce T-cell differentiation was evaluated. DCregs express C1q and FcgRIII and promote Treg development [13], whereas DC2 express CD141, GATA-3, OX40 ligand, and RIPK4 and promote the polarization of naive T-cells toward Th2 lymphocytes [89]. The expression of these biomarkers in peripheral mononuclear cells can be assessed during AIT. During sublingual AIT with grass pollen allergens, the change in molecular markers of DCs after 2 and 4 months of therapy correlated with the clinical effect of AIT. The use of these five biomarkers in the analysis will help with the identification of clinical responders and non-responders [89, 90].

AIT changes the methylation patterns of genes, and the products of these genes are involved in the pathogenesis of allergic reactions. This indicator can be a potential biomarker of the clinical efficacy of AIT if the relationship between AIT efficacy and changes in gene methylation during AIT will be established [27, 31, 91]. microRNA (miRNA) molecules and their effect on gene regulation are another candidate epigenetic marker. miR-3935 binds to the mRNA region encoding the prostaglandin EP3 receptor, inhibiting its expression. Sputum miR-3935 increased in patients with allergic asthma following AIT with grass allergens [92].

In vivo biomarkers

Provocation tests performed before and after AIT can be used as in vivo biomarkers. Provocation tests include subcutaneous and intradermal tests and nasal, conjunctival, and bronchial provocation tests [4]. The intensity of the allergic reaction following intradermal and nasal tests with grass pollen allergens decreased following subcutaneous and sublingual AIT. A correlation was also noted between symptom intensity after the provocation test and during the pollen season of causative plants [21, 83]. However, in vivo biomarkers do not have a predictive function and can only be used for the retrospective assessment of therapy efficacy [22].

CONCLUSION

AIT, a unique method of allergy therapy, can change the nature of the immune response and the clinical course of the disease. Cellular and molecular mechanisms of AIT must be examined not only from the fundamental medical science standpoint but also from that of routine clinical practice. A deep understanding of AIT mechanisms that affect various links in the pathogenesis of an allergic reaction opens up opportunities for exploring the associations between certain biomarkers and the clinical effect of AIT. It also helps in providing a personalized approach to therapy prescription and monitoring the efficacy of treatment over time. However, the currently described biomarkers have candidate status, and none of them are widely used in actual clinical practice. Thus, possible ways to determine AIT efficacy must be further evaluated. Reproducible research methods that would make it possible to implement the data obtained in scientific laboratories into the routine clinical practice of allergologists are warranted.

ADDITIONAL INFORMATION

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REFERENCES

1. Federal clinical guidelines for allergen-specific immunotherapy. Russian Association of Allergology and Clinical Immunology; 2013. (In Russ). Available from: https://raaci.ru/dat/pdf/7asit.pdf. Accessed: 15.02.2023.

2. Muraro A, Roberts G. Translating knowledge into clinical practice Allergen Immunotherapy Guidelines Part 1: Systematic reviews. European Academy of Allergy and Clinical Immunology (EAACI), 2017. 192 p.

3. Gushchin IS, Kurbacheva OM. Allergy and allergen-specific immunotherapy. Moscow: Farmus Print Media; 2010. (In Russ).

4. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: An EAACI Position Paper. *Allergy*. 2017;72(8):1156–1173. doi: 10.1111/ALL.13138

5. Sözener ZC, Mungan D, Cevhertas L. Tolerance mechanisms in allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2020;20(6):591–601. doi: 10.1097/ACI.0000000000000693

6. Kanagaratham C, Ansari Y, Lewis O, et al. IgE and IgG antibodies as regulators of mast cell and basophil functions in food allergy. *Front Immunol.* 2020;(11):603050. doi: 10.3389/fimmu.2020.603050

7. Schmid J, Würtzen P, Siddhuraj P, et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. *Allergy*. 2021;76(5):1528–1538. doi: 10.1111/ALL.14264

8. Eljaszewicz A, Ruchti F, Radzikowska U, et al. Trained immunity and tolerance in innate lymphoid cells, monocytes, and dendritic cells during allergen-specific immunotherapy. *J Allergy Clin Immunol.* 2021;147(5):1865–1877. doi: 10.1016/J.JACI.2020.08.042

9. Wen H, Qu L, Zhang Y, et al. A dendritic cells-targeting nano-vaccine by coupling polylactic-co-glycolic acid-encapsulated allergen with mannan induces regulatory T cells. *Int Arch Allergy Immunol*. 2021;182(9):777–787. doi:10.1159/000512872

10. Sirvent S, Soria I, Cirauqui C, et al. Novel vaccines targeting dendritic cells by coupling allergoids to nonoxidized mannan enhance allergen uptake and induce functional regulatory T cells through programmed death ligand 1. *J Allergy Clin Immunol*. 2016; 138(2):558–567.e11. doi: 10.1016/J.JACI.2016.02.029

11. Soria I, López-Relaño J, Viñuela M, et al. Oral myeloid cells uptake allergoids coupled to mannan driving Th1/Treg responses upon sublingual delivery in mice. *Allergy*. 2018;73(4):875–884. doi: 10.1111/ALL.13396

12. Benito-Villalvilla C, Pérez-Diego M, Angelina A, et al. Allergoid-mannan conjugates imprint tolerogenic features in human macrophages. *Allergy*. 2022;77(1):320–323. doi: 10.1016/J.JACI.2021.06.012

13. Zimmer A, Bouley J, Le Mignon M, et al. A regulatory dendritic cell signature correlates with the clinical efficacy of allergen-specific sublingual immunotherapy. *J Allergy Clin Immunol*. 2012; 129(4):1020–1030. doi: 10.1016/J.JACI.2012.02.014

14. Starchenka S, Heath M, Lineberry A, et al. Transcriptome analysis and safety profile of the early-phase clinical response to an adjuvanted grass allergoid immunotherapy. *World Allergy Organ.* 2019;12(11):100087. doi: 10.1016/J.WAOJOU.2019.100087

15. López J, Imam M, Satitsuksanoa P, et al. Mechanisms and biomarkers of successful allergen-specific immunotherapy. *Asia Pac Allergy*. 2022;12(4):e45. doi: 10.5415/apallergy.2022.12.e45

16. Wambre E, Delong J, James E, et al. Differentiation stage determines pathologic and protective allergen-specific CD4+ T-cell outcomes during specific immunotherapy. *J Allergy Clin Immunol*. 2012;129(2):544–551,551.e1-7. doi: 10.1016/J.JACI.2011.08.034

17. Wambre E, Delong J, James E, et al. Specific immunotherapy modifies allergen-specific CD4(+) T-cell responses in an epitope-dependent manner. *J Allergy Clin Immunol*. 2014;133(3):872–879.e7. doi: 10.1016/J.JACI.2013.10.054

18. Wambre E. Effect of allergen-specific immunotherapy on CD4+ T cells. *Curr Opin Allergy Clin Immunol*. 2015;15(6):581–587. doi: 10.1097/ACI.0000000000000216

19. Dolch A, Kunz S, Dorn B, et al. IL-10 signaling in dendritic cells is required for tolerance induction in a murine model of allergic airway inflammation. *Eur J Immunol*. 2019;49(2):302–312. doi: 10.1002/EJI.201847883

20. Scadding G, Calderon M, Shamji M, et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: The GRASS randomized clinical trial. *JAMA*. 2017;317(6):615–625. doi: 10.1001/JAMA.2016.21040

21. Renand A, Shamji M, Harris K, et al. Synchronous immune alterations mirror clinical response during allergen immunotherapy. *J Allergy Clin Immunol*. 2018;141(5):1750–1760.e1. doi: 10.1016/J.JACI.2017.09.041

22. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017;140(6):1485–1498. doi: 10.1016/j.jaci.2017.10.010

23. Zemmour D, Zilionis R, Kiner E, et al. Single-cell gene expression reveals a landscape of regulatory T cell phenotypes shaped by the TCR. *Nat Immunol*. 2018;19(3):291–301. doi: 10.1038/S41590-018-0051-0

24. Scadding G, Shamji M, Jacobson M, et al. Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. *Clin Exp Allergy*. 2010; 40(4):598–606. doi: 10.1111/J.1365-2222.2010.03462.X

25. Van de Veen W, Akdis M. Tolerance mechanisms of allergen immunotherapy. *Allergy*. 2020;75(5):1017–1018. doi: 10.1111/ALL.14126

26. Boonpiyathad T, van de Veen W, Wirz O, et al. Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy. *J Allergy Clin Immunol*. 2019;143(3):1077–1086.e10. doi: 10.1016/J.JACI.2018.10.061

27. Wang CM, Chang CB, Wu SF. Differential DNA methylation in allergen-specific immunotherapy of asthma. *Cell Mol Immunol*. 2020;17(9):1017–1018. doi: 10.1038/s41423-020-0476-x

28. Timoshenko DO, Kofiadi IA, Gudima GO, Kurbacheva OM. Epigenetics of bronchial asthma. *Immunologiya*. 2021;42(2):93–101. (In Russ). doi: 10.33029/0206-4952-2021-42-2-93-101

29. Swamy R, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol*. 2012;130(1):215–224.e7. doi: 10.1016/j.jaci.2012.04.021

30. Syed A, Garcia M, Lyu S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol*. 2014;133(2):500–510. doi: 10.1016/J.JACI.2013.12.1037

31. Wang C, Chang C, Chan M, et al. Dust mite allergen-specific immunotherapy increases IL4 DNA methylation and induces Der p-specific T cell tolerance in children with allergic asthma. *Cell Mol Immunol*. 2018;15(11):963–972. doi: 10.1038/CMI.2017.26

32. Shamji M, Layhadi J, Achkova D, et al. Role of IL-35 in sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2019;143(3): 1131–1142.e4. doi: 10.1016/J.JACI.2018.06.041
33. Rigas D, Lewis G, Aron J, et al. Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction. *J Allergy Clin Immunol*. 2017;139(5): 1468–1477.e2. doi: 10.1016/J.JACI.2016.08.034
34. Shamji M, Larson D, Eifan A, et al. Differential induction of allergen-specific IgA responses following timothy grass subcutaneous and sublingual immunotherapy. *J Allergy Clin Immunol*. 2021;148(4):1061–1071.e11. doi: 10.1016/j.jaci.2021.03.030
35. Shamji M, Valenta R, Jardetzky T, et al. The role of allergen-specific IgE, IgG and IgA in allergic disease. *Allergy*. 2021;76(12): 3627–3641. doi: 10.1111/ALL.14908
36. Van de Veen W, Akdis M. Role of IgG4 in IgE-mediated allergic responses. *J Allergy Clin Immunol*. 2016;138(5):1434–1435. doi: 10.1016/J.JACI.2016.07.022
37. Orengo J, Radin A, Kamat V, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. *Nat Commun*. 2018;9(1):1421. doi: 10.1038/S41467-018-03636-8
38. Kolfschoten M, Schuurman J, Losen M, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science*. 2007;317(5844):1554–1557. doi: 10.1126/SCIENCE.1144603
39. Heeringa J, McKenzie C, Varese N, et al. Induction of IgG2 and IgG4 B-cell memory following sublingual immunotherapy for ryegrass pollen allergy. *Allergy*. 2020;75(5):1121–1132. doi: 10.1111/ALL.14073
40. Boonpiyathad T, Pradubpongsa P, Mitthamsiri W, et al. Allergen-specific immunotherapy boosts allergen-specific IgD production in house dust mite-sensitized asthmatic patients. *Allergy*. 2020;75(6):1457–1460. doi: 10.1111/ALL.14133
41. Satitsuksanoa P, Daanje M, Akdis M, et al. Biology and dynamics of B cells in the context of IgE-mediated food allergy. *Allergy*. 2021;76(6):1707–1717. doi: 10.1111/ALL.14684
42. Jansen K, Cevhertas L, Ma S, et al. Regulatory B cells, A to Z. *Allergy*. 2021;76(9):2699–2715. doi: 10.1111/ALL.14763
43. Ma S, Satitsuksanoa P, Jansen K, et al. B regulatory cells in allergy. *Immunol Rev*. 2021;299(1):10–30. doi: 10.1111/IMR.12937
44. Van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol*. 2013;131(4):1204–1212. doi: 10.1016/J.JACI.2013.01.014
45. Boonpiyathad T, Meyer N, Moniuszko M, et al. High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers. *Allergy*. 2017;72(3): 407–415. doi: 10.1111/ALL.12966
46. Wang S, Xia P, Chen Y, et al. Regulatory innate lymphoid cells control innate intestinal inflammation. *Cell*. 2017;171(1):201–216.e18. doi: 10.1016/J.CELL.2017.07.027
47. Morita H, Kubo T, Rückert B, et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid. *J Allergy Clin Immunol*. 2019;143(6):2190–2201.e9. doi: 10.1016/J.JACI.2018.12.1018
48. Golebski K, Layhadi J, Sahiner U, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. *Immunity*. 2021;54(2): 291–307.e7. doi: 10.1016/J.IMMUNI.2020.12.013
49. Federal clinical guidelines for allergic rhinitis diagnosis and management. 2020. (In Russ). Available from: https://cr.minzdrav.gov.ru/recomend/261_1. Accessed: 15.02.2023.
50. Federal clinical guidelines for bronchial asthma diagnosis and management. 2021. (In Russ). Available from: https://cr.minzdrav.gov.ru/recomend/359_2. Accessed: 15.02.2023.
51. Shamji MH, Ljørring C, Würtzen PA. Predictive biomarkers of clinical efficacy of allergen-specific immunotherapy: How to proceed. *Immunotherapy*. 2013;5(3):203–206. doi: 10.2217/imt.13.6
52. Muraro A., Roberts G. Translating knowledge into clinical practice Allergen Immunotherapy Guidelines Part 2: Systematic reviews. European Academy of Allergy and Clinical Immunology (EAACI), 2017. 190 p.
53. Timoshenko DO, Pavlova KS, Kurbacheva OM, Ilina NI. Molecular allergology place in allergen-specific immunotherapy. *Russ J Allergy*. 2022;19(3):336–345. (In Russ). doi: 10.36691/RJA1572
54. Shamji M, Ljørring C, Francis J, et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. *Allergy*. 2012;67(2): 217–226. doi: 10.1111/J.1398-9995.2011.02745.X
55. Dahl R, Kapp A, Colombo G, et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol*. 2008;121(2):512–518.e2. doi: 10.1016/J.JACI.2007.10.039
56. Gleich G, Zimmermann E, Henderson L, et al. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: A six-year prospective study. *J Allergy Clin Immunol*. 1982;70(4):261–271. doi: 10.1016/0091-6749(82)90062-8
57. Pilette C, Nouri-Aria K, Jacobson M, et al. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-β expression. *J Immunol*. 2007;178(7):4658–4666. doi: 10.4049/JIMMUNOL.178.7.4658
58. Nouri-Aria K, Wachholz P, Francis J, et al. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. *J Immunol*. 2004;172(5):3252–3259. doi: 10.4049/JIMMUNOL.172.5.3252
59. Di Lorenzo G, Mansueto P, Pacor M, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;123(5): 1103–1110,1110.e1-4. doi: 10.1016/J.JACI.2009.02.012
60. Fujimura T, Yonekura S, Horiguchi S, et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clin Immunol*. 2011;139(1):65–74. doi: 10.1016/J.CLIM.2010.12.022
61. Würtzen P, Lund G, Lund K, et al. A double-blind placebo-controlled birch allergy vaccination study II: Correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation. *Clin Exp Allergy*. 2008;38(8):1290–1301. doi: 10.1111/J.1365-2222.2008.03020.X
62. Bohle B, Kinaciyan T, Gerstmayr M, et al. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol*. 2007;120(3):707–713. doi: 10.1016/J.JACI.2007.06.013
63. Ciepiela O, Zawadzka-Krajewska A, Kotuła I, et al. sublingual immunotherapy for asthma: Affects T-cells but does not impact basophil activation. *Pediatric Allergy Immunol Pulmonol*. 2014;27(1):17–23. doi: 10.1089/PED.2014.0328

64. Schulten V, Tripple V, Seumois G, et al. Allergen-specific immunotherapy modulates the balance of circulating Tfh and Tfr cells. *J Allergy Clin Immunol*. 2018;141(2):775–777.e6. doi: 10.1016/j.jaci.2017.04.032
65. Atkinson A, Colburn W, DeGruttola V, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89–95. doi: 10.1067/MCP.2001.113989
66. Shamji M, Wilcock L, Wachholz P, et al. The IgE-facilitated allergen binding (FAB) assay: Validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. *J Immunol Methods*. 2006;317(1-2):71–79. doi: 10.1016/J.JIM.2006.09.004
67. Shamji M, Francis J, Würtzen P, et al. Cell-free detection of allergen-IgE cross-linking with immobilized phase CD23: Inhibition by blocking antibody responses after immunotherapy. *J Allergy Clin Immunol*. 2013;132(4):1003–1005.e1-4. doi: 10.1016/J.JACI.2013.05.025
68. Liu J, Hu M, Tao X, et al. Salivary IgG4 levels contribute to assessing the efficacy of dermatophagoides pteronyssinus subcutaneous immunotherapy in children with asthma or allergic rhinitis. *J Clin Med*. 2023;12(4):1665. doi: 10.3390/JCM12041665
69. Knol E, Mul F, Jansen H, et al. Monitoring human basophil activation via CD63 monoclonal antibody 435. *J Allergy Clin Immunol*. 1991;88(3):328–338. doi: 10.1016/0091-6749(91)90094-5
70. Ebo D, Bridts C, Mertens C, et al. Analyzing histamine release by flow cytometry (HistaFlow): A novel instrument to study the degranulation patterns of basophils. *J Immunol Method*s. 2012; 375(1-2):30–38. doi: 10.1016/j.jim.2011.09.003
71. Nullens S, Sabato V, Faber M, et al. Basophilic histamine content and release during venom immunotherapy: Insights by flow cytometry. *Cytometry B Clin Cytom*. 2013;84B(3):173–178. doi: 10.1002/CYTO.B.21084
72. Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol*. 2003;33(5):1205–1214. doi: 10.1002/EJI.200322919
73. Faith A, Richards D, Verhoef A, et al. Impaired secretion of interleukin-4 and interleukin-13 by allergen-specific T cells correlates with defective nuclear expression of NF-AT2 and jun B: relevance to immunotherapy. *Clin Exp Allergy*. 2003;33(9):1209–1215. doi: 10.1046/J.1365-2222.2003.01748.X
74. Ebner C, Siemann U, Bohle B, et al. Immunological changes during specific immunotherapy of grass pollen allergy: Reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen. *Clin Exp Allergy*. 1997;27(9):1007–1015. doi: 10.1111/J.1365-2222.1997.TB01252.X
75. Fanta C, Bohle B, Hirt W, et al. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. *Int Arch Allergy Immunol*. 1999;120(3):218–224. doi: 10.1159/000024270
76. Cosmi L, Santarlasci V, Angeli R, et al. Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. *Clin Exp Allergy*. 2006; 36(3):261–272. doi: 10.1111/J.1365-2222.2006.02429.X
77. Wachholz P, Nouri-Aria K, Wilson D, et al. Grass pollen immunotherapy for hayfever is associated with increases in local nasal but not peripheral Th1:Th2 cytokine ratios. *Immunology*. 2002;105(1):56–62. doi: 10.1046/J.1365-2567.2002.01338.X
78. Francis JN, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+T cells by grass pollen immunotherapy. *J Allergy Clin Immunol*. 2003; 111(6):1255–1261. doi: 10.1067/mai.2003.1570
79. Plewako H, Holmberg K, Oancea I, et al. A follow-up study of immunotherapy-treated birch-allergic patients: Effect on the expression of chemokines in the nasal mucosa. *Clin Exp Allergy*. 2008;38(7):1124–1131. doi: 10.1111/J.1365-2222.2008.03005.X
80. Makino Y, Noguchi E, Takahashi N, et al. Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2010;126(6):1163–1169.e5. doi: 10.1016/J.JACI.2010.06.031
81. Li H, Xu E, He M. Cytokine responses to specific immunotherapy in house dust mite-induced allergic rhinitis patients. *Inflammation*. 2015;38(6):2216–2223. doi: 10.1007/S10753-015-0204-3
82. Sakashita M, Yamada T, Imoto Y, et al. Long-term sublingual immunotherapy for Japanese cedar pollinosis and the levels of IL-17A and complement components 3a and 5a. *Cytokine*. 2015; 75(1):181–185. doi: 10.1016/J.CYTO.2015.03.019
83. Scadding G, Eifan A, Lao-Araya M, et al. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. *Allergy*. 2015;70(6): 689–696. doi: 10.1111/ALL.12608
84. Ciprandi G, De Amici M, Murdaca G, et al. Adipokines and sublingual immunotherapy: Preliminary report. *Hum Immunol*. 2009;70(1):73–78. doi: 10.1016/J.HUMIMM.2008.10.001
85. Kirmaz C, Kirgiz O, Bayrak P, et al. Effects of allergen-specific immunotherapy on functions of helper and regulatory T cells in patients with seasonal allergic rhinitis. *Eur Cytokine Netw*. 2011;22(1):15–23. doi: 10.1684/ECN.2011.0277
86. Xie S, Jiang S, Zhang H, et al. Prediction of sublingual immunotherapy efficacy in allergic rhinitis by serum metabolomics analysis. *Int Immunopharmacol*. 2021;(90):107211. doi: 10.1016/J.INTIMP.2020.107211
87. Zheng P, Yan G, Zhang Y, et al. Metabolomics reveals process of allergic rhinitis patients with single- and double-species mite subcutaneous immunotherapy. *Metabolites*. 2021;11(9):613. doi: 10.3390/METABO11090613
88. Shamji M, Layhadi J, Perera-web A, et al. IL-35+ Regulatory T Cells suppress grass pollen-driven Th2 responses and are induced following grass pollen-specific sublingual immunotherapy. *J Allergy Clin Immunol*. 2013;131(2):AB146. doi: 10.1016/J.JACI.2012.12.1182
89. Gueguen C, Bouley J, Moussu H, et al. Changes in markers associated with dendritic cells driving the differentiation of either TH2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy. *J Allergy Clin Immunol*. 2016;137(2): 545–558. doi: 10.1016/j.jaci.2015.09.015
90. O'Mahony L, Akdis CA, Eiwegger T. Innate mechanisms can predict successful allergy immunotherapy. *J Allergy Clin Immunol*. 2016;137(2):559–561. doi: 10.1016/J.JACI.2015.10.047
91. Wang C, Chang C, Lee S, et al. Differential DNA methylation profiles of peripheral blood mononuclear cells in allergic asthmatic children following dust mite immunotherapy. *J Microbiol Immunol Inf*. 2020;53(6):986–995. doi: 10.1016/j.jmii.2020.06.004
92. Jakwerth C, Chaker A, Guerth F, et al. Sputum microRNA-screening reveals Prostaglandin EP3 receptor as selective target in allergen-specific immunotherapy. *Clin Exp Allergy*. 2021;51(12): 1577–1591. doi: 10.1111/CEA.14013

СПИСОК ЛИТЕРАТУРЫ

1. Федеральные клинические рекомендации по проведению аллергенспецифической иммунотерапии. Российская ассоциация аллергологов и клинических иммунологов, 2013. Режим доступа: https://raaci.ru/dat/pdf/7asit.pdf. Дата обращения: 15.02.2023.

2. Muraro A., Roberts G. Translating knowledge into clinical practice Allergen Immunotherapy Guidelines Part 1: Systematic reviews. European Academy of Allergy and Clinical Immunology (EAACI), 2017. 192 p.

3. Гущин И.С., Курбачева О.М. Аллергия и аллергенспецифическая иммунотерапия. Москва: Фармус Принт Медиа, 2010.

4. Shamji M., Kappen J. H., Akdis M., et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: An EAACI Position Paper // Allergy. 2017. Vol. 72, N 8. P. 1156–1173. doi: 10.1111/ALL.13138

5. Sözener Z.C., Mungan D., Cevhertas L. Tolerance mechanisms in allergen immunotherapy // Curr Opin Allergy Clin Immunol. 2020. Vol. 20, N 6. P. 591–601. doi: 10.1097/ACI.0000000000000693

6. Kanagaratham C., Ansari Y., Lewis O., et al. IgE and IgG antibodies as regulators of mast cell and basophil functions in food allergy // Front Immunol. 2020. N 11. P. 603050. doi: 10.3389/fimmu.2020.603050

7. Schmid J., Würtzen P., Siddhuraj P., et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients // Allergy. 2021. Vol. 76, N 5. P. 1528–1538. doi: 10.1111/ALL.14264

8. Eljaszewicz A., Ruchti F., Radzikowska U., et al. Trained immunity and tolerance in innate lymphoid cells, monocytes, and dendritic cells during allergen-specific immunotherapy // J Allergy Clin Immunol. 2021. Vol. 147, N 5. P. 1865–1877. doi: 10.1016/J.JACI.2020.08.042

9. Wen H., Qu L., Zhang Y., et al. A dendritic cells-targeting nanovaccine by coupling polylactic-co-glycolic acid-encapsulated allergen with mannan induces regulatory T cells // Int Arch Allergy Immunol. 2021. Vol. 182, N 9. P. 777–787. doi: 10.1159/000512872

10. Sirvent S., Soria I., Cirauqui C., et al. Novel vaccines targeting dendritic cells by coupling allergoids to nonoxidized mannan enhance allergen uptake and induce functional regulatory T cells through programmed death ligand 1 // J Allergy Clin Immunol. 2016. Vol. 138, N 2. P. 558–567.e11. doi: 10.1016/J.JACI.2016.02.029

11. Soria I., López-Relaño J., Viñuela M., et al. Oral myeloid cells uptake allergoids coupled to mannan driving Th1/Treg responses upon sublingual delivery in mice // Allergy. 2018. Vol. 73, N 4. P. 875–884. doi: 10.1111/ALL.13396

12. Benito-Villalvilla C., Pérez-Diego M., Angelina A., et al. Allergoid-mannan conjugates imprint tolerogenic features in human macrophages // Allergy. 2022. Vol. 77, N 1. P. 320–323. doi: 10.1016/J.JACI.2021.06.012

13. Zimmer A., Bouley J., Le Mignon M., et al. A regulatory dendritic cell signature correlates with the clinical efficacy of allergen-specific sublingual immunotherapy // J Allergy Clin Immunol. 2012. Vol. 129, N 4. P. 1020–1030. doi: 10.1016/J.JACI.2012.02.014

14. Starchenka S., Heath M., Lineberry A., et al. Transcriptome analysis and safety profile of the early-phase clinical response to an adjuvanted grass allergoid immunotherapy // World Allergy Organ. 2019. Vol. 12, N 11. P. 100087. doi: 10.1016/J.WAOJOU.2019.100087

15. López J., Imam M., Satitsuksanoa P., et al. Mechanisms and biomarkers of successful allergen-specific immunotherapy // Asia Pac Allergy. 2022. Vol. 12, N 4. P. e45. doi: 10.5415/apallergy.2022.12.e45

16. Wambre E., Delong J., James E., et al. Differentiation stage determines pathologic and protective allergen-specific CD4+ T-cell outcomes during specific immunotherapy // J Allergy Clin Immunol. 2012. Vol. 129, N 2. P. 544–551,551.e1-7. doi: 10.1016/J.JACI.2011.08.034

17. Wambre E., Delong J., James E., et al. Specific immunotherapy modifies allergen-specific CD4(+) T-cell responses in an epitope-dependent manner // J Allergy Clin Immunol. 2014. Vol. 133, N 3. P. 872–879.e7. doi: 10.1016/J.JACI.2013.10.054

18. Wambre E. Effect of allergen-specific immunotherapy on CD4+ T cells // Curr Opin Allergy Clin Immunol. 2015. Vol. 15, N 6. P. 581–587. doi: 10.1097/ACI.0000000000000216

19. Dolch A., Kunz S., Dorn B., et al. IL-10 signaling in dendritic cells is required for tolerance induction in a murine model of allergic airway inflammation // Eur J Immunol. 2019. Vol. 49, N 2. P. 302–312. doi: 10.1002/EJI.201847883

20. Scadding G., Calderon M., Shamji M., et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: The GRASS randomized clinical trial // JAMA. 2017. Vol. 317, N 6. P. 615–625. doi: 10.1001/JAMA.2016.21040

21. Renand A., Shamji M., Harris K., et al. Synchronous immune alterations mirror clinical response during allergen immunotherapy // J Allergy Clin Immunol. 2018. Vol. 141, N 5. P. 1750-1760.e1. doi: 10.1016/J.JACI.2017.09.041

22. Shamji M.H., Durham S.R. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers // J Allergy Clin Immunol. 2017. Vol. 140, N 6. P. 1485–1498. doi: 10.1016/j.jaci.2017.10.010

23. Zemmour D., Zilionis R., Kiner E., et al. Single-cell gene expression reveals a landscape of regulatory T cell phenotypes shaped by the TCR // Nat Immunol. 2018. Vol. 19, N 3. P. 291–301. doi: 10.1038/S41590-018-0051-0

24. Scadding G., Shamji M., Jacobson M., et al. Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells // Clin Exp Allergy. 2010. Vol. 40, N 4. P. 598–606. doi: 10.1111/J.1365-2222.2010.03462.X

25. Van de Veen W., Akdis M. Tolerance mechanisms of allergen immunotherapy // Allergy. 2020. Vol. 75, N 5. P. 1017–1018. doi: 10.1111/ALL.14126

26. Boonpiyathad T., van de Veen W., Wirz O., et al. Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy // J Allergy Clin Immunol. 2019. Vol. 143, N 3. P. 1077–1086.e10. doi: 10.1016/J.JACI.2018.10.061

27. Wang C.M., Chang C.B., Wu S.F. Differential DNA methylation in allergen-specific immunotherapy of asthma // Cell Mol Immunol. 2020. Vol. 17, N 9. P. 1017–1018. doi: 10.1038/s41423-020-0476-x

28. Тимошенко Д.О., Кофиади И.А., Гудима Г.О., Курбачева О.М. Эпигенетика бронхиальной астмы // Иммунология. 2021. Т. 42. № 2. С. 93–101. doi: 10.33029/0206-4952-2021-42-2-93-101

29. Swamy R., Reshamwala N., Hunter T., et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy // J Allergy Clin Immunol. 2012. Vol. 130, N 1. P. 215–224.e7. doi: 10.1016/j.jaci.2012.04.021

30. Syed A., Garcia M., Lyu S., et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3) // J Allergy Clin Immunol. 2014. Vol. 133, N 2. P. 500–510. doi: 10.1016/J.JACI.2013.12.1037
31. Wang C., Chang C., Chan M., et al. Dust mite allergen-specific immunotherapy increases IL4 DNA methylation and induces Der p-specific T cell tolerance in children with allergic asthma // Cell Mol Immunol. 2018. Vol. 15, N 11. P. 963–972. doi: 10.1038/CMI.2017.26
32. Shamji M., Layhadi J., Achkova D., et al. Role of IL-35 in sublingual allergen immunotherapy // J Allergy Clin Immunol. 2019. Vol. 143, N 3. P. 1131–1142.e4. doi: 10.1016/J.JACI.2018.06.041
33. Rigas D., Lewis G., Aron J., et al. Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction // J Allergy Clin Immunol. 2017. Vol. 139, N 5. P. 1468–1477.e2. doi: 10.1016/J.JACI.2016.08.034
34. Shamji M., Larson D., Eifan A., et al. Differential induction of allergen-specific IgA responses following timothy grass subcutaneous and sublingual immunotherapy // J Allergy Clin Immunol. 2021. Vol. 148, N 4. P. 1061–1071.e11. doi: 10.1016/j.jaci.2021.03.030
35. Shamji M., Valenta R., Jardetzky T., et al. The role of allergen-specific IgE, IgG and IgA in allergic disease // Allergy. 2021. Vol. 76, N 12. P. 3627–3641. doi: 10.1111/ALL.14908
36. Van de Veen W., Akdis M. Role of IgG4 in IgE-mediated allergic responses // J Allergy Clin Immunol. 2016. Vol. 138, N 5. P. 1434–1435. doi: 10.1016/J.JACI.2016.07.022
37. Orengo J., Radin A., Kamat V., et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement // Nat Commun. 2018. Vol. 9, N 1. P. 1421. doi: 10.1038/S41467-018-03636-8
38. Kolfschoten M., Schuurman J., Losen M., et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange // Science. 2007. Vol. 317, N 5844. P. 1554–1557. doi: 10.1126/SCIENCE.1144603
39. Heeringa J., McKenzie C., Varese N., et al. Induction of IgG2 and IgG4 B-cell memory following sublingual immunotherapy for ryegrass pollen allergy // Allergy. 2020. Vol. 75, N 5. P. 1121–1132. doi: 10.1111/ALL.14073
40. Boonpiyathad T., Pradubpongsa P., Mitthamsiri W., et al. Allergen-specific immunotherapy boosts allergen-specific IgD production in house dust mite-sensitized asthmatic patients // Allergy. 2020. Vol. 75, N 6. P. 1457–1460. doi: 10.1111/ALL.14133
41. Satitsuksanoa P., Daanje M., Akdis M., et al. Biology and dynamics of B cells in the context of IgE-mediated food allergy // Allergy. 2021. Vol. 76, N 6. P. 1707–1717. doi: 10.1111/ALL.14684
42. Jansen K., Cevhertas L., Ma S., et al. Regulatory B cells, A to Z // Allergy. 2021. Vol. 76, N 9. P. 2699–2715. doi: 10.1111/ALL.14763
43. Ma S., Satitsuksanoa P., Jansen K., et al. B regulatory cells in allergy // Immunol Rev. 2021. Vol. 299, N 1. P. 10–30. doi: 10.1111/IMR.12937
44. Van de Veen W., Stanic B., Yaman G., et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses // J Allergy Clin Immunol. 2013. Vol. 131, N 4. P. 1204–1212. doi: 10.1016/J.JACI.2013.01.014
45. Boonpiyathad T., Meyer N., Moniuszko M., et al. High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers // Allergy. 2017. Vol. 72, N 3. P. 407–415. doi: 10.1111/ALL.12966
46. Wang S., Xia P., Chen Y., et al. Regulatory innate lymphoid cells control innate intestinal inflammation // Cell. 2017. Vol. 171, N 1. P. 201–216.e18. doi: 10.1016/J.CELL.2017.07.027
47. Morita H., Kubo T., Rückert B., et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid // J Allergy Clin Immunol. 2019. Vol. 143, N 6. P. 2190–2201.e9. doi: 10.1016/J.JACI.2018.12.1018
48. Golebski K., Layhadi J., Sahiner U., et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response // Immunity. 2021. Vol. 54, N 2. P. 291–307.e7. doi: 10.1016/J.IMMUNI.2020.12.013
49. Федеральные клинические рекомендации по диагностике и лечению аллергического ринита. 2020. Режим доступа: https://cr.minzdrav.gov.ru/recomend/261_1. Дата обращения: 15.02.2023.
50. Федеральные клинические рекомендации по диагностике и лечению бронхиальной астмы. 2021. Режим доступа: https://cr.minzdrav.gov.ru/recomend/359_2. Дата обращения: 15.02.2023.
51. Shamji M.H., Ljørring C., Würtzen P.A. Predictive biomarkers of clinical efficacy of allergen-specific immunotherapy: How to proceed // Immunotherapy. 2013. Vol. 5, N 3. P. 203–206. doi: 10.2217/imt.13.6
52. Muraro A., Roberts G. Translating knowledge into clinical practice Allergen Immunotherapy Guidelines Part 2: Systematic reviews. European Academy of Allergy and Clinical Immunology (EAACI), 2017. 190 p.
53. Тимошенко Д.О., Павлова К.С., Курбачёва О.М., Ильина Н.И. Место молекулярной аллергодиагностики при проведении аллерген-специфической иммунотерапии // Российский аллергологический журнал. 2022. Т. 19, № 3. С. 336–345. doi: 10.36691/RJA1572
54. Shamji M., Ljørring C., Francis J., et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy // Allergy. 2012. Vol. 67, N 2. P. 217–226. doi: 10.1111/J.1398-9995.2011.02745.X
55. Dahl R., Kapp A., Colombo G., et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years // J Allergy Clin Immunol. 2008. Vol. 121, N 2. P. 512–518.e2. doi: 10.1016/J.JACI.2007.10.039
56. Gleich G., Zimmermann E., Henderson L., et al. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: A six-year prospective study // J Allergy Clin Immunol. 1982. Vol. 70, N 4. P. 261–271. doi: 10.1016/0091-6749(82)90062-8
57. Pilette C., Nouri-Aria K., Jacobson M., et al. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-β expression // J Immunol. 2007. Vol. 178, N 7. P. 4658–4666. doi: 10.4049/JIMMUNOL.178.7.4658
58. Nouri-Aria K., Wachholz P., Francis J., et al. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity // J Immunol. 2004. Vol. 172, N 5. P. 3252–3259. doi: 10.4049/JIMMUNOL.172.5.3252
59. Di Lorenzo G., Mansueto P., Pacor M., et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy // J Allergy Clin Immunol. 2009. Vol. 123, N 5. P. 1103–1110,1110.e1-4. doi: 10.1016/J.JACI.2009.02.012

60. Fujimura T., Yonekura S., Horiguchi S., et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis // Clini Immunol. 2011. Vol. 139, N 1. P. 65–74. doi: 10.1016/J.CLIM.2010.12.022

61. Würtzen P., Lund G., Lund K., et al. A double-blind placebo-controlled birch allergy vaccination study II: Correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation // Clin Exp Allergy. 2008. Vol. 38, N 8. P. 1290–1301. doi: 10.1111/J.1365-2222.2008.03020.X

62. Bohle B., Kinaciyan T., Gerstmayr M., et al. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation // J Allergy Clin Immunol. 2007. Vol. 120, N 3. P. 707–713. doi: 10.1016/J.JACI.2007.06.013

63. Ciepiela O., Zawadzka-Krajewska A., Kotuła I., et al. Sublingual immunotherapy for asthma: Affects T-cells but does not impact basophil activation // Pediatric Allergy Immunol Pulmonol. 2014. Vol. 27, N 1. P. 17–23. doi: 10.1089/PED.2014.0328

64. Schulten V., Tripple V., Seumois G., et al. Allergen-specific immunotherapy modulates the balance of circulating Tfh and Tfr cells // J Allergy Clin Immunol. 2018. Vol. 141, N 2. P. 775–777.e6. doi: 10.1016/j.jaci.2017.04.032

65. Atkinson A., Colburn W., DeGruttola V., et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework // Clin Pharmacol Ther. 2001. Vol. 69, N 3. P. 89–95. doi: 10.1067/MCP.2001.113989

66. Shamji M., Wilcock L., Wachholz P., et al. The IgE-facilitated allergen binding (FAB) assay: Validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses // J Immunol Methods. 2006. Vol. 317, N 1-2. P. 71–79. doi: 10.1016/J.JIM.2006.09.004

67. Shamji M., Francis J., Würtzen P., et al. Cell-free detection of allergen-IgE cross-linking with immobilized phase CD23: Inhibition by blocking antibody responses after immunotherapy // J Allergy Clin Immunol. 2013. Vol. 132, N 4. P. 1003–1005.e1-4. doi: 10.1016/J.JACI.2013.05.025

68. Liu J., Hu M., Tao X., et al. Salivary IgG4 levels contribute to assessing the efficacy of dermatophagoides pteronyssinus subcutaneous immunotherapy in children with asthma or allergic rhinitis // J Clin Med. 2023. Vol. 12, N 4. P. 1665. doi: 10.3390/JCM12041665

69. Knol E., Mul F., Jansen H., et al. Monitoring human basophil activation via CD63 monoclonal antibody 435 // J Allergy Clin Immunol. 1991. Vol. 88, N 3. P. 328–338. doi: 10.1016/0091-6749(91)90094-5

70. Ebo D., Bridts C., Mertens C., et al. Analyzing histamine release by flow cytometry (HistaFlow): A novel instrument to study the degranulation patterns of basophils // J Immunol Methods. 2012. Vol. 375, N 1-2. P. 30–38. doi: 10.1016/j.jim.2011.09.003

71. Nullens S., Sabato V., Faber M., et al. Basophilic histamine content and release during venom immunotherapy: Insights by flow cytometry // Cytometry B Clin Cytom. 2013. Vol. 84B, N 3. P. 173–178. doi: 10.1002/CYTO.B.21084

72. Jutel M., Akdis M., Budak F., et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy // Eur J Immunol. 2003. Vol. 33, N 5. P. 1205–1214. doi: 10.1002/EJI.200322919

73. Faith A., Richards D., Verhoef A., et al. Impaired secretion of interleukin-4 and interleukin-13 by allergen-specific T cells correlates with defective nuclear expression of NF-AT2 and jun B: Relevance to immunotherapy // Clin Exp Allergy. 2003. Vol. 33, N 9. P. 1209–1215. doi: 10.1046/J.1365-2222.2003.01748.X

74. Ebner C., Siemann U., Bohle B., et al. Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen // Clin Exp Allergy. 1997. Vol. 27, N 9. P. 1007–1015. doi: 10.1111/J.1365-2222.1997.TB01252.X

75. Fanta C., Bohle B., Hirt W., et al. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy // Int Arch Allergy Immunol. 1999. Vol. 120, N 3. P. 218–224. doi: 10.1159/000024270

76. Cosmi L., Santarlasci V., Angeli R., et al. Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production // Clin Exp Allergy. 2006. Vol. 36, N 3. P. 261–272. doi: 10.1111/J.1365-2222.2006.02429.X

77. Wachholz P., Nouri-Aria K., Wilson D., et al. Grass pollen immunotherapy for hayfever is associated with increases in local nasal but not peripheral Th1:Th2 cytokine ratios // Immunology. 2002. Vol. 105, N 1. P. 56–62. doi: 10.1046/J.1365-2567.2002.01338.X

78. Francis J.N., Till S.J., Durham S.R. Induction of IL-10+CD4+CD25+T cells by grass pollen immunotherapy // J Allergy Clin Immunol. 2003. Vol. 111, N 6. P. 1255–1261. doi: 10.1067/mai.2003.1570

79. Plewako H., Holmberg K., Oancea I., et al. A follow-up study of immunotherapy-treated birch-allergic patients: effect on the expression of chemokines in the nasal mucosa // Clin Exp Allergy. 2008. Vol. 38, N 7. P. 1124–1131. doi: 10.1111/J.1365-2222.2008.03005.X

80. Makino Y., Noguchi E., Takahashi N., et al. Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis // J Allergy Clin Immunol. 2010. Vol. 126, N 6. P. 1163–1169.e5. doi: 10.1016/J.JACI.2010.06.031

81. Li H., Xu E., He M. Cytokine responses to specific immunotherapy in house dust mite-induced allergic rhinitis patients // Inflammation. 2015. Vol. 38, N 6. P. 2216–2223. doi: 10.1007/S10753-015-0204-3

82. Sakashita M., Yamada T., Imoto Y., et al. Long-term sublingual immunotherapy for Japanese cedar pollinosis and the levels of IL-17A and complement components 3a and 5a // Cytokine. 2015. Vol. 75, N 1. P. 181–185. doi: 10.1016/J.CYTO.2015.03.019

83. Scadding G., Eifan A., Lao-Araya M., et al. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge // Allergy. 2015. Vol. 70, N 6. P. 689–696. doi: 10.1111/ALL.12608

84. Ciprandi G., De Amici M., Murdaca G., et al. Adipokines and sublingual immunotherapy: Preliminary report // Hum Immunol. 2009. Vol. 70, N 1. P. 73–78. doi: 10.1016/J.HUMIMM.2008.10.001

85. Kirmaz C., Kirgiz O., Bayrak P., et al. Effects of allergen-specific immunotherapy on functions of helper and regulatory T cells in patients with seasonal allergic rhinitis // Eur Cytokine Netw. 2011. Vol. 22, N 1. P. 15–23. doi: 10.1684/ECN.2011.0277

86. Xie S., Jiang S., Zhang H., et al. Prediction of sublingual immunotherapy efficacy in allergic rhinitis by serum metabolomics analysis // Int Immunopharmacol. 2021. N 90. P. 107211. doi: 10.1016/J.INTIMP.2020.107211

87. Zheng P., Yan G., Zhang Y., et al. Metabolomics reveals process of allergic rhinitis patients with single- and double-species mite subcutaneous immunotherapy // Metabolites. 2021. Vol. 11, N 9. P. 613. doi: 10.3390/METABO11090613
88. Shamji M., Layhadi J., Perera-web A., et al. IL-35+ Regulatory T Cells suppress grass pollen-driven Th2 responses and are induced following grass pollen-specific sublingual immunotherapy // J Allergy Clin Immunol. 2013. Vol. 131, N 2. P. AB146. doi: 10.1016/j.jaci.2012.12.1182
89. Gueguen C., Bouley J., Moussu H., et al. Changes in markers associated with dendritic cells driving the differentiation of either TH2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy // J Allergy Clin Immunol. 2016. Vol. 137, N 2. P. 545–558. doi: 10.1016/j.jaci.2015.09.015
90. O'Mahony L., Akdis C.A., Eiwegger T. Innate mechanisms can predict successful allergy immunotherapy // J Allergy Clin Immunol. 2016. Vol. 137, N 2. P. 559–561. doi: 10.1016/J.JACI.2015.10.047
91. Wang C., Chang C., Lee S., et al. Differential DNA methylation profiles of peripheral blood mononuclear cells in allergic asthmatic children following dust mite immunotherapy // J Microbiol Immunol Inf. 2020. Vol. 53, N 6. P. 986–995. doi: 10.1016/j.jmii.2020.06.004
92. Jakwerth C., Chaker A., Guerth F., et al. Sputum microRNA-screening reveals Prostaglandin EP3 receptor as selective target in allergen-specific immunotherapy // Clin Exp Allergy. 2021. Vol. 51, N 12. P. 1577–1591. doi: 10.1111/CEA.14013

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