

DOI: <https://doi.org/10.36691/RJA1389>

Molecular allergodiagnosics capabilities in determining the indications for allergen-specific immunotherapy with house dust mites allergen and its effectiveness in atopic dermatitis patients

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BACKGROUND: Atopic dermatitis (AD) is a widespread chronic inflammatory skin disease, in the development of which complex genetic and immune mechanisms, environmental factors, allergens, are involved. An effective method of treating IgE-mediated allergic diseases is allergen-specific immunotherapy (ASIT), which affects all pathogenetically significant links of the allergic process. It is known that as a result of ASIT tissue sensitivity to an allergen, nonspecific tissue hyper-reactivity and the intensity of allergic inflammation decrease, which testifies to the rearrangement of the cellular response from Th2 to Th1 with a corresponding change in the cytokine profile. Currently, dozens of scientific papers on the efficacy and safety of subcutaneous and sublingual ASIT in AD have been published; however, the question of the advisability of its appointment still remains unresolved.

AIM: To investigate the ASIT with house dust mite (HDM) allergens efficacy in AD patients, considering the results of molecular allergy diagnosis.

MATERIALS AND METHODS: The study was conducted as a prospective comparative open study, including 32 patients with AD (20 children and 12 adults), 90.6% were diagnosed with concomitant respiratory allergic diseases. Molecular allergodiagnosics was performed using microchip technology with purified natural or recombinant allergen components immobilized in the solid phase (Immuno-Solid phase Allergen Chip, ISAC) to quantify allergen-specific IgE (asIgE) against 112 allergen molecules from 51 allergen sources in one study (ImmunoCAP ISAC (ThermoFisher, Phadia, Uppsala, Sweden). Patients were divided into two groups depending on the profile of molecular sensitization: with the presence or absence of asIgE to the major allergens of *D. farinae* and/or *D. pteronyssinus* Der p 1 (p 2) and/or Der f 1 (f 2). All patients passed three consecutive courses of subcutaneous ASIT with water-salted HDM allergens produced by I.I. Mechnikov Biomed (Russia) under an accelerated scheme for 3 years. To assess the severity of the disease, the SCORAD indices, the Investigator's Global Assessment (IGA), and the dermatological quality of life index (DLQI) were used.

RESULTS: Patients with sensitization to major allergens of *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2) more often achieved a significant improvement of AD symptoms according to the SCORAD index (OR 3.929, 95% CI: 0.879; 17.56), as well as they more often achieved IGA values of 1 or 0 after three courses of ASIT (OR 3.556, CI 95% 0.730–17.324) and more often assessed the effectiveness of ASIT as excellent and good in comparison with patients without sensitization to these components. The median and interquartile range of the DLQI index before treatment in group 1 was 17 [14; 20] points, in group 2 – 14 [12; 18], after the 3rd course of ASIT: 6 [2; 10] and 8 [3; 10] points in groups 1 and 2, respectively. Adverse events were rare, their frequency did not significantly differ in both groups.

CONCLUSION: ASIT with HDM allergens is an effective and safe method of treatment of AD patients. Determination of the molecular spectrum of sensitization to HDM allergens components allows to justify the indications and predict the effectiveness of ASIT.

Keywords: atopic dermatitis, molecular allergy diagnosis, allergen specific immunotherapy, house dust mites

For citation: Shtyrbul O.V., Dvornikov A.S., Khaitov M.R., Elisyutina O.G., Fedenko E.S. Molecular allergodiagnosics capabilities in determining the indications for allergen-specific immunotherapy with house dust mites allergen and its effectiveness in atopic dermatitis patients. *Russian Journal of Allergy*. 2020;17(3):82–92. DOI: <https://doi.org/10.36691/RJA1389>

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Статья поступила 22.05.2020 г.
Received: 22.05.2020.

Принята к печати 24.06.2020 г.
Accepted: 24.06.2020.

Рекомендована к публикации
Е.И. Гребенченко

Возможности молекулярной аллергодиагностики в определении показаний к аллерген-специфической иммунотерапии аллергеном клещей домашней пыли и ее эффективность у больных атопическим дерматитом

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ОБОСНОВАНИЕ: Атопический дерматит (АтД) – широко распространенное хроническое воспалительное заболевание кожи, в развитии которого принимают участие сложные генетические и иммунные механизмы, факторы окружающей среды, в первую очередь аллергены. Эффективным методом лечения IgE-опосредованных аллергических заболеваний является аллерген-специфическая иммунотерапия (АСИТ), которая воздействует на все патогенетически значимые звенья аллергического процесса. Известно, что в результате АСИТ формируется снижение тканевой чувствительности к аллергену, снижается неспецифическая тканевая гиперреактивность, уменьшается интенсивность аллергического воспаления, что свидетельствует в пользу перестройки клеточного ответа с Th2- на Th1-ответ с соответствующим изменением цитокинового профиля. В настоящее время опубликованы десятки научных работ, посвященных изучению эффективности и безопасности подкожной и сублингвальной АСИТ при АтД; вместе с тем вопрос о целесообразности ее назначения до сих пор остается нерешенным.

ЦЕЛЬ: Оценить эффективность аллерген-специфической иммунотерапии (АСИТ) аллергенами клещей домашней пыли (КДП), назначенной больным атопическим дерматитом (АтД) с учетом результатов молекулярной аллергодиагностики

МАТЕРИАЛЫ И МЕТОДЫ: Исследование проведено как проспективное сравнительное открытое, включены 32 пациента с АтД (20 детей и 12 взрослых), у 90,6% диагностированы сопутствующие респираторные аллергические заболевания. Молекулярная аллергодиагностика выполнена с применением технологии микрочипов с иммобилизованными на твердой фазе очищенными природными или рекомбинантными компонентами аллергенов (Immuno-Solid phase Allergen Chip, ISAC) для количественного определения аллерген-специфических IgE (asIgE) против 112 аллергенных молекул из 51 источника аллергенов в одном исследовании (ImmunoCAP ISAC (ThermoFisher, Phadia, Uppsala, Швеция). Пациенты были разделены на две группы в зависимости от профиля молекулярной сенсibilизации: с наличием или отсутствием asIgE к мажорным аллергенам КДП *D. farinae* и/или *D. pteronyssinus* Der p 1 (p 2) и/или Der f 1 (f 2). Для проведения АСИТ использовали водно-солевые аллергены *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* производства ОАО «Биомед» им. И.И. Мечникова (Россия). Всем пациентам проведено три последовательных курса АСИТ аллергенами клещей домашней пыли по ускоренной схеме в течение 3 лет. Для оценки тяжести течения заболевания были использованы индексы SCORAD, исследовательская глобальная оценка (Investigator's Global Assessment – IGA), дерматологический индекс качества жизни (ДИКЖ).

РЕЗУЛЬТАТЫ: После проведения трех последовательных курсов АСИТ аллергеном КДП пациенты, имеющие сенсibilизацию к мажорным аллергенам *D. farinae* и/или *D. pteronyssinus* Der p 1 (f 1) и/или Der p 2 (f 2), чаще достигали значительного уменьшения выраженности симптомов АтД на основании оценки индекса SCORAD (ОШ 3,929, ДИ 95%: 0,879; 17, 56) и значения IGA (1 или 0 после проведения трех курсов АСИТ, ОШ 3,556, ДИ 95% 0,730–17,324) и оценивали эффективность АСИТ как отличную и хорошую по сравнению с пациентами без сенсibilизации к этим компонентам. Медиана и интерквартильный размах показателя ДИКЖ до лечения в группе 1 составили 17 [14; 20] баллов, в группе 2 – 14 [12; 18] баллов, после 3-го курса АСИТ: 6 [2; 10] и 8 [3; 10] баллов в группах 1 и 2 соответственно. Нежелательные явления на фоне проводимой терапии были редки, частота их встречаемости значимо не различалась в обеих группах.

ЗАКЛЮЧЕНИЕ: АСИТ аллергенами КДП является эффективным и безопасным методом лечения пациентов с АтД. Определение молекулярного спектра сенсibilизации к компонентам КДП позволяет обосновать показания и прогнозировать эффективность АСИТ.

Ключевые слова: атопический дерматит, молекулярная аллергодиагностика, аллерген-специфическая иммунотерапия, клещи домашней пыли

Для цитирования: Штырбул О.В., Дворников А.С., Хаитов М.Р., Елисютина О.Г., Феденко Е.С. Возможности молекулярной аллергодиагностики в определении показаний к аллерген-специфической иммунотерапии аллергеном клещей домашней пыли и ее эффективность у больных атопическим дерматитом // *Российский Аллергологический Журнал*. 2020. Т. 17. № 3. С. 82–92. DOI: <https://doi.org/10.36691/RJA1389>

Introduction

Atopic dermatitis (AD) is a widespread chronic inflammatory skin disease, in the development of which complex genetic and immune mechanisms, environmental factors, primarily allergens, are involved. AD significantly affects the quality of patients' life, often leading to disability. Numerous studies confirm the role of sensitization to allergens such as house dust mite allergens, pollen, fungi-microorganisms [1–3], and most patients develop polyvalent sensitization to a wide range of allergens. An effective method of treating IgE-mediated allergic diseases is allergen-specific immunotherapy (ASIT), which affects all pathogenetically significant links of the allergic process. It is known that as a result of ASIT tissue sensitivity to an allergen, nonspecific tissue hyperreactivity and the intensity of allergic inflammation decrease, which testifies to the rearrangement of the cellular response from Th2 to Th1 response with a corresponding change in the cytokine profile [4]. The use of ASIT in AD is actively discussed in the scientific community of allergists and dermatologists. Currently, dozens of scientific papers on the efficacy and safety of subcutaneous and sublingual ASIT in AD have been published [5–10]; however, the question of the advisability of its appointment still remains unresolved. ASIT is an expensive treatment that is usually carried out over a period of several years; determination of indications for such therapy, correct selection of patients and accurate determination of causal allergens are necessary factors for the treatment effectiveness. The key aspect of ASIT is specificity, which implies a change in the immune response to the allergen that was treated, therefore, the precise determination of the causative allergen causing AD symptoms is a prerequisite for the appointment of ASIT. In case of allergic rhinitis (AR), bronchial asthma (BA), as well as mild AD, a traditional allergy examination, including the collection of an allergy history, skin tests with allergen extracts, and, if indicated, provocation tests are sufficient to achieve this goal [11]. In some cases, the determination of a causal allergen is difficult. Thus, in patients with a chronic recurrent course of AD, when traditional allergy examination is impossible due to a permanent exacerbation of the disease, as well as in cases of discrepancy between the anamnesis data and the results of skin testing, it is difficult to determine the causal allergen by traditional methods. The same situation is observed with food allergy, especially among children with severe AD, when the consumption of a large number of foods causes severe exacerbations of the disease. In such cases, it is impossible to determine with a high degree of probability the very food allergens affecting the course of the disease in a particular patient using traditional methods.

A similar situation is observed in patients with AD who are sensitized to HDM allergens. House dust mite (*Der-*

matophagoides pteronyssinus) contains several allergenic proteins, the most clinically important are Der p 1, Der p 2, Der p 5, Der p 7, Der p 21, and Der p 23, sensitization to which is most often associated with clinical manifestations of allergic diseases. Diagnostic and therapeutic extracts of HDM allergens differ in the content of the main allergens and, as a rule, are standardized only for Der p 1 and Der p 2 [12]. However, in clinical practice, patients are not always sensitized to major allergens, it turned out that sensitization to certain allergen molecules and their combinations can be associated with various clinical manifestations of allergy. It has been shown that the HDM molecules Der p 11 and Der p 18, which are components of the bodies of mites, are more often recognized by specific asIgE in patients with AD, while the molecules that belong to the fecal particles of the mite Der p 1, Der p 2, Der p 5, Der p 23, are more often recognized in patients with bronchial asthma [13]. Allergists in their practice often encounter a situation when a patient with AD has a positive skin test result with a diagnostic extract of HDM, laboratory diagnostics determine asIgE to HDM extracts, and MA using ISAC determine asIgE to tropomyosin Der p 10 rather than to major allergens Der p 1, 2/Der f 1, 2. This may be due to cross-reactivity to tropomyosin from other sources, and not true sensitization to HDM. With such a result of the diagnosis of ASIT with an allergen, the HDM will most likely be ineffective [14]. Moreover, the ineffectiveness of ASIT may also be due to the quality of allergens: not all commercial extracts are uniform in composition and quantity of major allergens and in protein levels, their concentration can vary from low to high values [12]. Determination at the molecular level of allergens to which IgE antibodies are produced makes it possible to select individual therapeutic preparations for ASIT, but in practice this is not always feasible.

The purpose of this study was to assess the effectiveness of ASIT with HDM allergens in patients with AD, taking into account the results of molecular allergy diagnostics.

Materials and methods

The study was conducted as a prospective open-label comparative study.

Study inclusion criteria:

- men or women at the age of 5–60;
- confirmed diagnosis of AD in accordance with generally accepted international criteria [15] with or without respiratory manifestations of allergy – AR and/or BA;
- confirmed sensitization to HDM allergens based on history data, skin test results and/or the availability of asIgE antibodies to HDM allergen extracts;
- availability of the results of the ISAC ImmunoCAP study;

– conducting at least three consecutive completed courses of ASIT with water-salt solutions of HDM allergens on an accelerated basis for 3 years.

Study exclusion criteria:

– inability of the patient or his legal representatives to adequately perceive the investigator's guidelines on the study procedure;

– history of severe somatic diseases (severe cardiovascular disease, renal and/or liver failure, cancer);

– disagreement of the patient to participate in the study.

Allergy examination methods

Allergy examination included:

1. Collecting an allergy history:

- history of present illness;
- history of respiratory manifestations of atopy;
- family history of allergic diseases;
- pharmacological history;
- food history;
- history of concomitant skin infection and other foci of chronic infection.

2. Skin prick tests with standard domestic sets of household, epidermal, pollen and food allergens produced by I.I. Mechnikov Biomed. Prick tests were performed and evaluated according to the guidelines for the diagnostic use of non-bacterial allergens according to a common method.

3. Quantification of total IgE in blood serum by enzyme-linked immunosorbent assay using LabodiaXema test systems (Switzerland – Russia).

4. Molecular allergy diagnostics was performed using microchip technology with purified natural or recombinant allergen components immobilized on the solid phase (Immuno-Solid phase Allergen Chip, ISAC), to quantify allergen-specific asIgE against 112 allergenic molecules from 51 allergen sources in one study (ImmunoCAP ISAC (Thermofisher, Phadia, Uppsala, Sweden). Test results are determined semi-quantitatively in ISAC Standardized Units (ISU). asIgE ≥ 0.3 ISU is considered a positive result.

32 patients (20 children and 12 adults) were selected in accordance with the inclusion and exclusion criteria at the premises of the Department of Allergy and Immunopathology of the NRC Institute of Immunology FMBA of Russia during four years from 2016 to 2019. The mean age (with standard deviation) was 18.28 ± 12.85 years. 8 out of 32 patients (7 children and 1 adult) had a mild course of AD, moderate severity – in 6 patients (4 children and 2 adults) and a severe course of the disease was diagnosed in 18 patients (9 children and 9 adults).

In 29 (90.6%) patients, concomitant respiratory allergic diseases were diagnosed: allergic rhinitis in 29 (90.6%) patients and in 12 (37.5%) atopic bronchial

asthma in combination with AR. Allergy examination in all patients confirm sensitization to household allergens: HDM *D. farinae* and/or *D. pteronyssinus*. In 31 (96.9%) patients an increase in the level of total IgE was revealed (Me 1495 [Q₁ 422; Q₃ 3910]).

To determine the molecular indications for prescribing ASIT and assess its effectiveness, we divided patients into 2 groups depending on the profile of molecular sensitization: with or without asIgE to major allergens of house dust mites *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2) (Fig. 1).

Before the start of ASIT, all patients underwent AD exacerbation treatment, external therapy (topical glucocorticosteroids (TGCS), topical calcineurin inhibitors (TCI), emollients) was selected. The use of antihistamines in therapeutic doses recommended for children and adults was also allowed.

To carry out ASIT, we used water-salt allergens *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, produced by I.I. Mechnikov Biomed (Russia). The preparations are a water-salt solution of protein-polysaccharide complexes obtained from mites *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* by adsorption on benzoic acid. ASIT was performed in patients with AD during the period of clinical or drug remission by an accelerated method in a hospital setting according to a previously developed scheme approved in the instruction for medical use.

All patients received three accelerated courses of ASIT with house dust mite allergens for three consecutive years.

To assess the severity of the course of the disease, we used the indices most often used in scientific and clinical practice:

1. Severity scoring of AD – SCORAD.

The severity scoring of atopic dermatitis (SCORAD) semi-quantitative scale was used to assess the severity of AD [16]. This scale combines objective (intensity and prevalence of skin lesions) and subjective (intensity of nighttime pruritus and sleep disturbance) criteria. In addition, the frequency of exacerbations of AD for 1 year was assessed. The average number of relapses of exacerbations of AD in each study group was assessed.

2. Investigator's Global Assessment – IGA. The severity of skin lesions is assessed on a 5-point scale, where 0 points corresponds to the absence of rashes, and 4 points to the most intense rashes [17].

3. Dermatology Life Quality Index (DLQI) in adults and children. Patients or their legal representatives independently filled out a special questionnaire, which is widely used in dermatology and validated to assess the impact of a dermatological disease on the patient's quality of life. The questionnaire consists of 10 questions, for each answer there are points from 0 to 3. The questions differ in the questionnaires for children and adults. Interpretation of the index: 0–1 points – AD has no effect

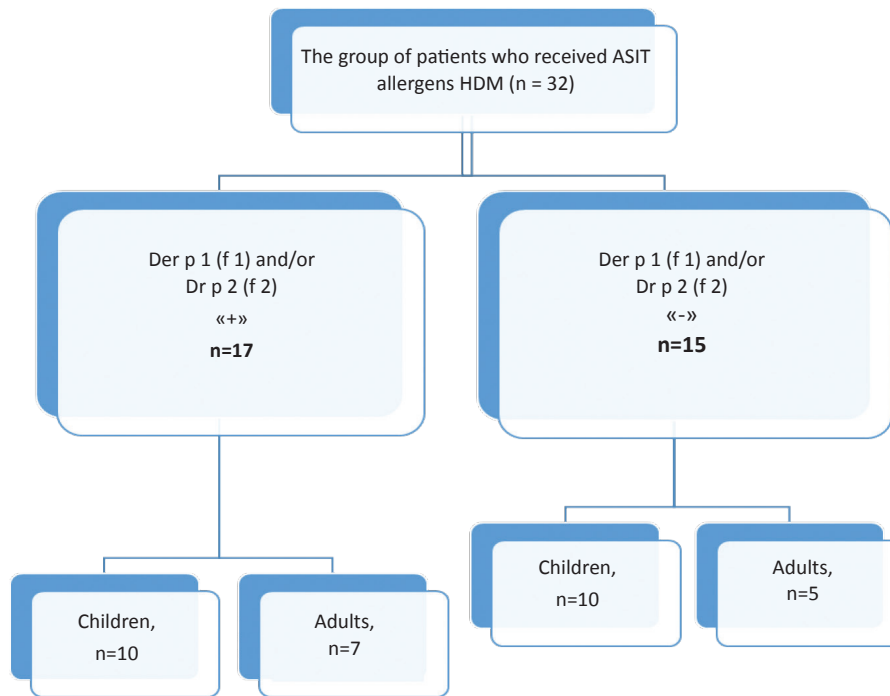


Figure 1. Distribution of AD patients (n=32) who received ASIT with house dust mite allergens, depending on the profile of molecular sensitization and age

on the patient's life; 2–5 points – AD has little effect on the patient's life; 6–10 points – AD has a moderate effect on the patient's life; 11–20 points – AD has a very strong effect on the patient's life; 21–30 points – AD has an extremely strong effect on the patient's life [18].

We also evaluated the following indicators during treatment:

- Assessment of the need for drug therapy on a 4-point scale – from 0 to 3 points:

- 0 points – no need for medication;
- 1 point – use of the drug 1–2 times a month;
- 2 points – use of the drug 1–2 times a week;
- 3 points – daily intake of the drug.

The need for the use of antihistamines and topical GCS was assessed separately. The number of patients who refused to use TGCS after treatment was also assessed.

- The patient's overall assessment of the therapy effectiveness.

The patient filled out a special questionnaire answering the question “How do you assess your condition after the last visit to the doctor?”

- Complete improvement of the condition – improvement 100% – “5 points”.
- Excellent condition – improvement 75–99% – “4 points”.
- Good condition – improvement 50–74% – “3 points”.
- Satisfactory condition – improvement 25–49% – “2 points”.
- Slight improvement – improvement 1–24% – “1 point”.

- No changes – improvement 0% – “0 points”.
- The condition worsened – “–1 point”.

The indices were assessed four times: before the first, second and third courses of treatment and 6–8 months after the third course of ASIT.

Statistical analysis

To describe the sample distribution of quantitative traits, the following indicators were used: median (Me) and upper (Q1) and lower quartiles (Q3) (interquartile range). Groups were compared using a nonparametric Mann-Whitney U-test to compare performance between two independent groups. The odds ratio OR is given with a 95% confidence interval (CI). The results were processed using the Statistica version 12.0 and SPSS Statistics version 17.0 software.

Results

As a result of ASIT with house dust mite allergens in most patients of both study groups, a significant improvement in the course of AD was achieved: the intensity and number of rashes, skin itching and frequency of disease relapses decreased; the quality of life has improved. Figures 2–5 show the change in SCORAD, IGA, frequency of AD relapses and DLQI. Over the course of three years of treatment, the majority of patients in both groups showed positive dynamics of the state of the skin with an improvement of varying severity. Figure 2 shows the number of patients who showed a 75% decrease in SCORAD (SCORAD 75) during treatment. After the 3rd course of ASIT, this

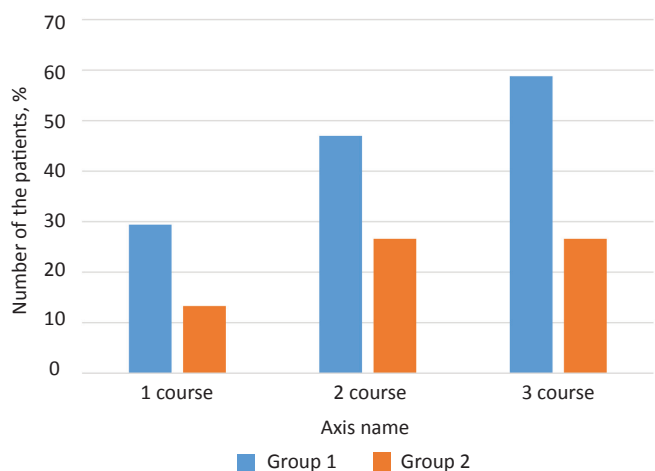


Figure 2. The number of patients who achieved an improvement in SCORAD by 75% during ASIT with house dust mite allergens

value was achieved in 10 (58.8%) patients in group 1 and in 4 (26.6%) patients in group 2. Thus, patients with sensitization to major allergens *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2) more often achieved a significant reduction in clinical manifestations of AD (OR 3.929, 95% CI 0.879; 17.56).

The same tendency was established when assessing IGA: before the start of ASIT, there were no significant statistical differences between the groups, Me [Q₁; Q₃] was initially 2.5 [2; 4] and 3 [2; 4], respectively. During treatment, there was a gradual decrease in the median of this indicator in both groups, while the number of patients who reached a value of 1 or 0 after three courses of ASIT was higher in group 1 than in group 2: 8 (47%) and 3 (20%), respectively (OR 3.556, 95% CI 0.730–17.324).

Figure 3 shows the dynamics of changes in this indicator during ASIT.

During the three-year period of treatment, most patients showed not only an improvement in the condition of the skin, but also a decrease in the number of relapses of the disease per year. Figure 4 shows the median relapse

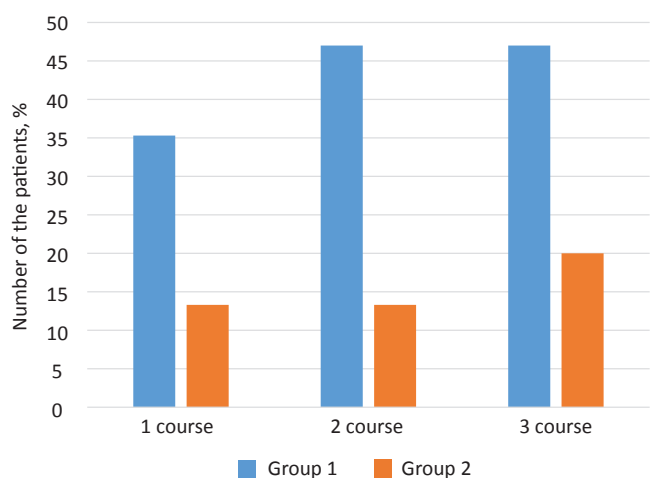


Figure 3. The number of patients who achieved IGA of 0 or 1 during ASIT with house dust mite allergens

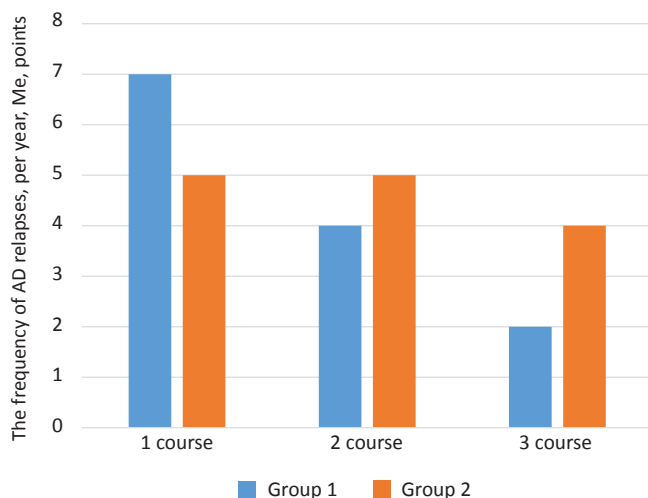


Figure 4. Change in the median frequency of AD relapses per year in patients of groups 1 and 2 during ASIT with HDM allergens

rates for 1, 2, and 3 years of follow-up in patients of both groups receiving ASIT.

We also evaluated the effect of the therapy on the quality of life of children and adults with AD. For this, we evaluated the DLQI for children and adults. Patients in both groups noted an improvement in the quality of life during the follow-up period, no significant differences between the groups before and during treatment were found (Fig. 5).

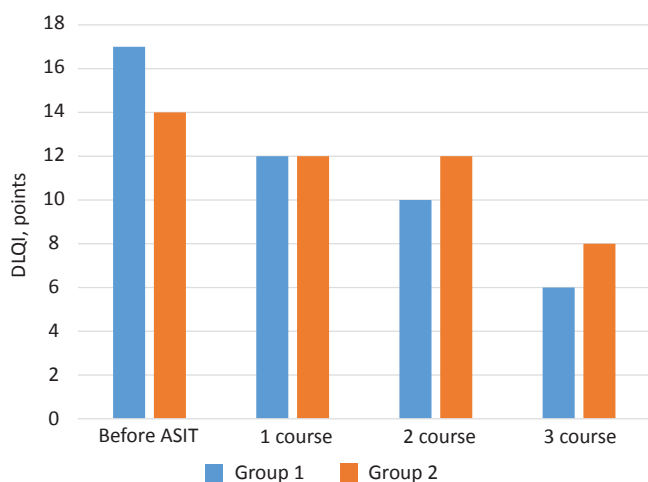


Figure 5. Changes in DLQI (Me) during ASIT in patients of groups 1 and 2

During ASIT, the majority of patients showed a decrease in the need for TGCS and antihistamines; no significant differences were found between the groups.

The patient also assessed the effectiveness of the therapy on a 7-point scale, where 5 points were regarded as complete improvement of the condition (100%), and the deterioration of the condition as – 1.

Table 1 shows the distribution of patients (%) of both groups, depending on the overall assessment of the effectiveness of the therapy before and during ASIT.

Table 1. Results of assessing the effectiveness of ASIT in patients with AD (n=32)

Patient groups Number of patients (%)	General assessment of the effectiveness of ASIT, points						
	5 Complete improvement of the condi- tion	4 Excellent condition	3 Good condi- tion	2 Satisfactory condition	1 Minor im- provement	0 Without changes	-1 Condition has worsened
After the 1 st course of ASIT							
Group 1	0	1 (5.8)	5 (29.4)	4 (23.5)	3 (17.6)	2 (11.8)	1(5.8)
Group 2	0	0	4 (26.7)	6 (40)	4 (26.7)	1 (6.7)	0
After the 2 nd course of ASIT							
Group 1	0	3 (17.6)	2 (11.8)	4 (23.5)	6 (35.3)	2 (11.8)	0
Group 2	0	3 (20)	4 (26.7)	2 (13.3)	4 (26.7)	2 (13.3)	0
After the 3 rd course of ASIT							
Group 1	1 (5.8)	5 (29.4)	4 (23.5)	4 (23.5)	3 (17.6)	0	0
Group 2	0	3 (20)	3 (20)	5 (33.3)	2 (13.3)	2 (13.3)	0

Thus, after the 3rd course of ASIT, most patients from group 1 assessed the effect of the treatment as good, excellent and complete improvement – 10 (58.8%) patients, while in group 2 the number of such patients was only 6 (40%) OR 2.143, 95% CI 0.521–8.814.

In addition to efficacy, we also assessed the safety of ASIT in our patients based on the incidence and nature of adverse events. As you know, during ASIT in response to the introduction of an allergen, undesirable side effects in the form of local or systemic reactions can develop. Local reactions were observed in most patients and were expressed by redness, itching, edema at the injection site of the allergen. Local reactions were resolved on their own within a day. In the presence of significant local reactions, we changed the allergen administration scheme, increasing the intervals between the next injections, and additionally prescribed 2nd generation H₁-antihistamines, the use of which does not affect the effectiveness of ASIT. Systemic reactions were rare, within a few minutes after the injection of the allergen and, in rare cases, after 30 minutes. During ASIT, our patients did not have severe systemic reactions, mild systemic reactions were manifested by nasal congestion, sneezing, itching in the nose, itchy eyelids, red eyes, lacrimation, sore throat and dry cough. Also in 2 patients the appearance of headache,

temperature rise to subfebrile digits was noted (Table 2).

Thus, patients with sensitization to major allergens *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2) more often achieved a significant improvement in the clinical manifestations of AD according to SCORAD (OR 3.929, 95% CI 0.879; 17.56); more often reached IGA of 1 or 0 after three courses of ASIT (OR 3.556, 95% CI 0.730–17.324). In addition, patients with sensitization to major allergens *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2) more often assessed the effectiveness of ASIT as excellent and good compared with patients without sensitization to these components. Adverse events during therapy were rare, and their frequency did not differ significantly in both groups.

Discussion of results and conclusion

The results of our study demonstrate the efficacy and safety of ASIT in patients with AD under the condition of proven sensitization to HDM allergens. The literature data on the use of this method in AD are contradictory; in recent years, two systematic reviews devoted to this problem have been published. One of them presents data from a meta-analysis of randomized controlled studies published up to December 2012 on the effectiveness of

Table 2. Adverse events in patients of group 1 and group 2 during ASIT with house dust mite allergens

Adverse event	Group 1 Der p 1 (f 1) and/or Der p 2 (f 2) «+» n=17	Group 2 Der p 1 (f 1) and/or Der p 2 (f 2) «-» n=15
Local reactions, n (%)	10 (58,8)	8 (53,3)
Systemic reactions, n (%)		
Nasal stuffiness	2 (11,7)	1 (6,7)
Eye tearing, itching	2 (11,7)	1 (6,7)
Skin itching	4 (23,5)	5 (33,3)
Headache	1 (5,9)	0
Temperature rise to subfebrile digits	1 (5,9)	0

ASIT in AD. Eight randomized controlled studies were analyzed, involving a total of 385 people. It was found that ASIT has a significant positive effect on patients with AD [OR 5.35; 95% CI 1.61–17.77], ASIT demonstrated significant efficacy in long-term treatment (OR 6.42; 95% CI 1.31–7.48) and in severe AD (OR 3.13; 95% CI 1.31–7.48). A more significant positive effect of subcutaneous ASIT (OR 4.27; 95% CI 1.36–13.39) compared with sublingual was also shown. The results of this meta-analysis demonstrate a moderate level of evidence for the effectiveness of ASIT in AD (2c) [19]. In 2016, another Cochrane level review [20], which analyzed studies on the use of ASIT for AD published up to July 2015, was published. The analysis included only randomized, placebo-controlled studies using standardized preparations of extracts of allergens in patients with AD. The authors analyzed 12 such studies, which involved 733 people. 10 studies are devoted to ASIT with HDM allergens (6 studies – subcutaneous ASIT, 4 studies – sublingual ASIT) and 2 studies – ASIT with pollen allergens. In three studies (208 patients), there was no significant difference in assessing the severity of the course of the disease in the study groups compared to the control groups, OR 0.75 (95% CI 0.45, 1.26) was not found; the difference between symptoms was 0.74 on a 20-point scale (95% CI 1.98, 0.50). In two other studies (85 participants), on the contrary, there was a significant decrease in the symptoms of AD, which was reflected in a decrease in the global severity scoring of AD – OR 2.85 (95% CI 1.02, 7.96) and the scale of itching intensity, the difference in values was 4.20 on a 10-point scale (95% CI 3.69, 4.71). The meta-analysis was limited due to the significant heterogeneity of the

study groups. No significant adverse events have been described during ASIT in AD. The evidence base allowed us to recommend ASIT for the treatment of patients with AD with proven sensitization to HDM and/or to pollen allergens (the level of evidence and persuasiveness of the recommendations – 2a, B) [15].

An important feature of studies carried out in recent years is their focus on the development of new strategies in the context of precision medicine. The emergence of new diagnostic methods and determination of specific biomarkers of the disease allows for a deeper understanding of the pathogenetic mechanisms of AD and development of personalized approaches to patient management. Obviously, ASIT cannot be equally effective for all patients, since a personalized approach to the treatment of AD and development of an individual treatment regimen depending on the involvement of certain immune mechanisms in each case is required. A thorough identification of significant specific immunological and molecular allergy markers makes it possible to pre-select patients who need ASIT, which can significantly increase the effectiveness of therapy and develop personalized approaches to the diagnosis and treatment of AD. In our study, the effectiveness of ASIT was evaluated prospectively taking into account the data of molecular allergy diagnostics and the greatest effectiveness of ASIT was established in patients sensitized to the major allergens *D. farinae* (Derf 1, Derf 1) and/or *D. pteronyssinus* (Derp 1, Derp 2), however, ASIT was a fairly effective treatment method in both study groups. This phenomenon can be explained by the following reasons:

1. Patients of both groups showed positive results of allergy examination with extracts of allergens, but

patients of group 2 did not reveal sensitization to major components of HDM allergens *D. farinae* and/or *D. pteronyssinus* Der p 1 (f 1) and/or Der p 2 (f 2); perhaps they have sensitization to another major allergen, Der p 23, which was not previously available in the ISAC test.

2. Commercial extracts of allergens may contain minor and cross-reacting components, due to the action of which the positive effect of ASIT (to some extent) could be achieved.

3. A set of measures during ASIT, namely, long-term monitoring of the patient's condition, proper skin care, effective external therapy and elimination measures, including diets, allow you to control the treatment process and respond in time in case of deterioration, which in generally leads to a stable positive effect.

The results of our study confirm the efficacy and safety of ASIT with HDM allergens in patients with AD and demonstrate the possibility of using molecular biomarkers of sensitization to HDM allergens to predict the effectiveness of ASIT. For a more accurate determination of molecular indications for ASIT, further investigation and double-blind randomized studies involving a control group of patients are required.

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All authors were involved in the study and manuscript preparation and approved it before the publication.

Funding information

The study had no sponsorship.

Conflict of interest

All authors declare no conflicts of interest.

Участие авторов

Концепция и дизайн исследования – О.В. Штырбул, А.С. Дворников, О.Г. Елисютина, Е.С. Феденко; сбор и обработка материала – О.В. Штырбул, А.С. Дворников, О.Г. Елисютина, Е.С. Феденко; написание текста – О.В. Штырбул, О.Г. Елисютина, Е.С. Феденко; редактирование – Е.С. Феденко, М.Р. Хаитов. Все авторы внесли существенный вклад в проведение исследования и подготовку статьи, прочли и одобрили финальную версию до публикации.

Информация об источниках финансирования

Исследование не имело спонсорской поддержки.

Конфликт интересов

Авторы заявляют об отсутствии конфликта интересов.