

КЛИНИЧЕСКАЯ И ИММУНОЛОГИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ АМБРОЗИЙНОГО ПОЛЛИНОЗА В САМАРСКОЙ ОБЛАСТИ

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Резюме. Аллергический ринит и бронхиальная астма – широко распространенные респираторные аллергические заболевания. На некоторых территориях РФ доминирующей причиной поллиноза является амброзия. Целью исследования было оценить клиническую и иммунологическую эффективность АСИТ аллергеном *Ambrosia artemisiifolia* у пациентов, сенсибилизированных *Ambrosia trifida* в Самарской области. Пациентам с подтвержденной сенсибилизацией к амброзии трехраздельной была проведена иммунотерапия аллергоидом амброзии полыннолистной предсезонно. После лечения у пациентов было отмечено снижение степени выраженности симптомов аллергического ринита по ВАШ ($p = 0,00001$), снижение потребности в медикаментозных средствах ($p = 0,0003$), а также потребности в ГКС на фоне проводимой терапии с 34,6% до 0% ($p = 0,00001$). В 8% случаев результат лечения был хороший, в 69% – удовлетворительный, в 23% – неудовлетворительный. В группе контроля не было отмечено изменений степени выраженности симптомов ($p = 0,858$). Также в группе контроля потребность в лекарственных препаратах осталась без изменений и 14,3% пациентов продолжали использовать ГКС.

После АСИТ наблюдалось снижение уровня IL-4 ($p = 0,002$), и снижение соотношения IL-4/IL-10 ($p = 0,0063$); при этом изменения уровня остальных цитокинов (IL-10; IFN γ) оказались статистически незначимыми ($p > 0,05$). До лечения уровни IL-4/IL-10 в обеих группах были сопоставимы, а после лечения различия стали статистически значимы ($p = 0,031$). Мы не получили статистически-значимого изменения уровня IgG4 *Amb a 1*, IgG4 *Amb trifida*. Зависимости (корреляции) между уровнем отдельных цитокинов и результатами лечения получено не было. В результате проведенной АСИТ были получены положительные клинические и иммунологические результаты. У большинства пациентов заболевание приобрело контролируемое течение. При этом отсутствие отличных и низкое число хороших результатов АСИТ, вероятно, связано с внутривидовыми аллергенными свойствами амброзии.

Ключевые слова: амброзия, иммунотерапия, поллиноз, трифида, цитокины, IL-4, *Amb a 1*

CLINICAL AND IMMUNOLOGICAL EFFECTIVENESS OF TREATMENT OF RAGWEED POLLINOSIS IN THE SAMARA REGION

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Abstract. Allergic rhinitis and bronchial asthma are widespread respiratory allergic diseases. In some territories of the Russian Federation, the dominant cause of pollinosis is ragweed. The aim of the study was to

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evaluate the clinical and immunological efficacy of ASIT with the allergen *Ambrosia artemisiifolia* in patients sensitized to *Ambrosia trifida* in the Samara region. Patients with proven sensitization to *Ambrosia trifida* were held immunotherapy with *Ambrosia artemisiifolia* allergoid pre-season. After treatment, patients had a decrease in the severity of symptoms of allergic rhinitis according to VAS ($p = 0.00001$), a decrease in the need for medications ($p = 0.0003$), as well as the need for corticosteroids against the background of therapy from 34.6% to 0% ($p = 0.00001$). In 8% of cases, the result of treatment was good, in 69% satisfactory, in 23% unsatisfactory. In the control group, there were no changes in the severity of symptoms ($p = 0.858$). Also, in the control group, the need for medications remained unchanged and 14.3% of patients continued to use corticosteroids.

After ASIT, there was a decrease in the level of IL-4 ($p = 0.002$), and a decrease in the ratio of IL-4/IL-10 ($p = 0.0063$); at the same time, changes in the level of other cytokines (IL-10; IFN γ) were statistically insignificant ($p > 0.05$). Before treatment, the levels of IL-4/IL-10 in both groups were comparable, and after treatment, the differences became statistically significant ($p = 0.031$). We did not get a statistically significant change in the level of IgG4 *Amb a 1* or IgG4 *Amb trifida*. There was no correlation between the level of individual cytokines and the results of treatment. As a result of the conducted ASIT, positive clinical and immunological results were obtained. In most patients, the disease has acquired a controlled course. At the same time, the lack of excellent and low number of good results of ASIT is probably due to the intraspecific allergenic properties of ragweed.

Keywords: ragweed, immunotherapy, pollinosis, trifida, cytokines, IL-4, Amb a 1

Introduction

Allergic rhinitis (AR) and allergic bronchial asthma (BA) are chronic diseases of the respiratory tract, characterized by constant minimal inflammatory reactions due to exposure to allergens.

According to epidemiological studies, the adult BA prevalence in the Russian Federation is 6.9%, and AR – 6.5% [5].

In the Omsk region, 40% of all visits to an allergist are associated with symptoms of hay fever. In the Moscow region, percentage of hay fever in the structure of allergic diseases is 17.5% [8]. In the Dagestan, 40% of patients with hay fever revealed sensitization to weed allergens, among which wormwood and ragweed predominate. In the Stavropol region, up to 40% of the population suffers from hay fever, with ragweed being the dominant taxon of weed pollen [13].

For the treatment of hay fever and other respiratory allergic diseases, the method of allergen-specific immunotherapy (ASIT) has been used for many years. ASIT is the only method capable of curbing allergic inflammation and retarding transition of AR to BA, which implies improved quality of patients' life.

The aim of the study was to evaluate the clinical and immunological efficacy of ASIT with the ragweed (*Ambrosia artemisiifolia*) allergen in patients sensitized with *Ambrosia trifida* in the Samara region.

Materials and methods

There were enrolled patients ($n = 41$) with manifestations of pollinosis and confirmed sensitization to ragweed tripartite, in the absence of the main allergic component of ragweed *Ambrosia Amb a 1*. All patients were randomized into the study group ($n = 26$) and the control group ($n = 15$).

In some patients with hay fever in both groups they had concomitant manifestations of respiratory allergy in the form of year-round rhinitis (in 30.7% in the study group and 20% in the control group) and a combination with bronchial asthma (in 15.5% and 13.3% in the study and control groups, respectively). The average age of patients in the study and control group was 28.52 ± 12.07 and 32.8 ± 13.2 years, respectively. In the study group, the proportion of males and females was 42.3% and 57.7%, respectively; in the control group 20% and 80%, respectively.

The patients of the study group were treated with the ragweed allergen. Patients in the control group received symptomatic treatment.

Immunotherapy was carried out with a standardized ragweed allergoid 10.000 PNU/ml (NPO Microgen, Russia) pre-season, starting from a dilution of 1:10 000 0.1 ml subcutaneous at gradually escalating dose according to the instructions of the drug. The average total dose was 10 593 PNU.

All patients before and after treatment were assessed for the following parameters: IL-4, IL-10, IFN γ , IgE to *Amb. trifida*, allergic component *Amb a 1*, IgG4 *Amb a 1*, IgG-trifida. An enzyme-linked immunosorbent assay (ELISA) was used to determine serum cytokines and IgG4. The study of the level of specific IgE was carried out on Phadia 250 equipment using the ImmunoCap ISAC diagnostic test system (Sweden).

The scale for assessing nasal symptoms, taking into account the need for drug therapy, was analyzed according to the generally accepted method. The severity of AR symptoms was also assessed using the VAS: results from 0 to 50 indicate a controlled course of AR, from 50 and above an uncontrolled course of

AR [3, 9]. The results are presented as the median Me ($Q_{0.25}$ - $Q_{0.75}$).

Evaluation of immunotherapy effectiveness was carried out according to the modified scheme of A.D. Ado, wherein an excellent effect – no symptoms of hay fever during the dusting season and no use of drug therapy, a good effect – occurrence of minor symptoms of hay fever and no / minimal drug therapy, a satisfactory effect a decreased severity of pollinosis symptoms and lowered need for drug therapy, an unsatisfactory effect the absence of positive effects of treatment (the presence of the usual symptoms of hay fever and the previous need for symptomatic drugs).

Statistical data processing was carried out using generally accepted methods of variation statistics. Methods of nonparametric statistics were used, the Mann–Whitney U-test (U), Wilcoxon's W-test (W) and the cross-tabulation method (χ^2) were used. The critical value of the significance level was taken equal to 5%. The data obtained were processed using the application package AtteStat, version 10.5.1, statistical formulas of the Microsoft Excel program, version 5.0.

Results and discussion

Prevalence of ragweed sensitization

According to the results of studies carried out earlier in the Samara region, 75% patients suffering from hay fever were sensitized to weeds (mono- or in combination with other groups of pollen allergens). More than half of such patients (53.8%) were sensitized to ragweed. At the same time, patients with negative skin tests to ragweed, had IgE to *Ambrosia trifida* in 65.9% of cases, whereas in 13.6% of cases – a combination of IgE against two types of ragweed [15].

ASIT results (clinical effectiveness)

Patients with sensitization to *Ambrosia trifida* (n = 26) underwent pre-season ASIT with *Ambrosia artemisiifolia* allergoid according to the classical scheme.

During the ragweed dusting season, patients in the study group noted improved health condition: according to the VAS scale, the severity of AR symptoms before and after treatment was 70 (60-80) and 40 (30-50), respectively (T = 351; p = 0.00001). At the same time, in 8% of cases, the result of treatment was assessed as good, in the majority of patients (69%), the result was assessed as satisfactory, and in 23% of cases unsatisfactory results were obtained.

The need for drugs in patients receiving ASIT decreased from 2 (2-3) to 1 (1-2), (W = 120; p = 0.0003). The need for corticosteroids along with ongoing therapy (ASIT) in patients also decreased from 34.6% to 0% ($\chi^2 = 11$; p = 0.00001).

In the control group, no significant changes in the severity of symptoms within the study year vs. previous years were observed: the mean values on the VAS scale

were 65 (50-80) and 65 (55-80) in the current and last season of ragweed dusting, respectively (U = 88; p = 0.858). The need for drugs did not change and averaged 2 (1-2), (U = 98; p = 0.78), while 14.3% of patients continued to use glucocorticoids.

Despite the low percentage of good results and the absence of excellent ASIT results, we obtained positive treatment results, and in the majority of patients, the disease acquired a controlled course.

Effect of ASIT on cytokine levels (immunological efficacy)

We assessed the levels of serum cytokines (IL-4, IL-10) before and after treatment, and also diagnosed the level of IFN γ , which is an important marker of the Th1 immune response.

After the course of ASIT with the ragweed allergen in the active group, a significant decrease in the level of IL-4 from 36.19 to 20.19 pg/ml (W = 277; p = 0.002) was recorded; changes in the level of other cytokines (IL-10; IFN) were insignificant (p > 0.05) (Figure 1).

The level of IL-4 after treatment in the study group was also lower than that in the control group: 20.19 versus 51.79 pg/ml (W = 96.5; p = 0.0110).

The IL-4/IL-10 ratio after treatment in the study group decreased from 1.097 to 0.63 (W = 283; p = 0.0063), while in the control group it remained without significant changes (W = 35; p = 0.2719) (Figure 2). At the same time, before treatment, the levels of IL-4/IL-10 in both groups were comparable and reached 1.097 and 1.6 in the active group and control group (U = 232.5; p = 0.31), respectively, whereas after treatment the differences became statistically significant: 0.63 and 2.17, respectively (U = 258; p = 0.031).

The IL-4/IFN γ ratio in the study group did not change significantly after ASIT and reached 0.15 and 0.094 before and after immunotherapy, respectively (W = 254; p = 0.046). No relationship (correlation) between the level of individual cytokines (also their ratio) and the results of treatment was obtained.

Effect of ASIT on specific levels of IgE and IgG

After the treatment we found no significant change in the level of IgG4 *Amb a 1* (W = 90.5; p = 0.052), nor IgG4 *Amb trifida* (W = 131; p = 0.587). The IgE *Amb trifida* level in the study group did not change after treatment and was 14.4 vs 14.69 kUA/l before treatment (T = 150; p = 0.74).

It is believed that allergens of ragweed (mainly *Amb a1*) and *Ambrosia trifida* have strong crosslinkages and that one type of allergen is sufficient for the treatment of ragweed pollinosis [14]. The main component *Amb a 1* has a wide reactivity that exceeds and overlaps the levels of both isoallergens and allergens of related ragweed species. Many studies show a good efficacy of ragweed pollinosis specific immunotherapy (both sublingual and subcutaneous) with the ragweed allergen.

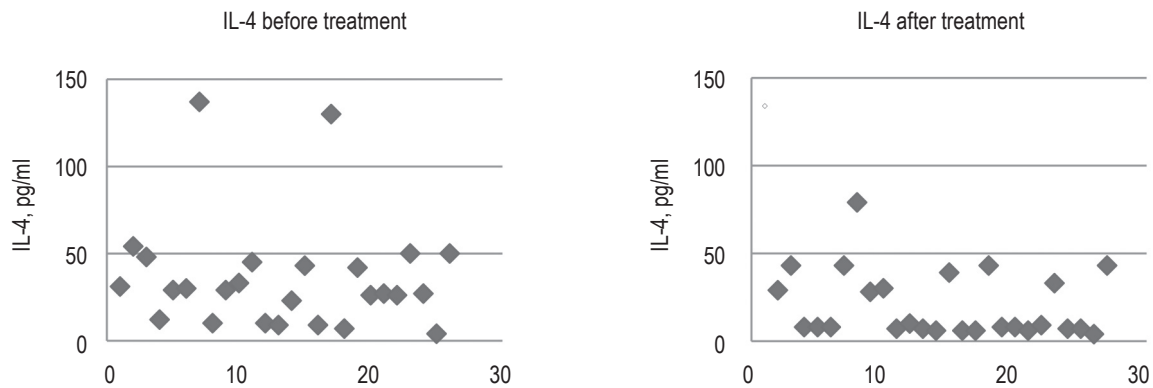


Figure 1. Levels of IL-4 in the study group before and after ASIT with ragweed allergen

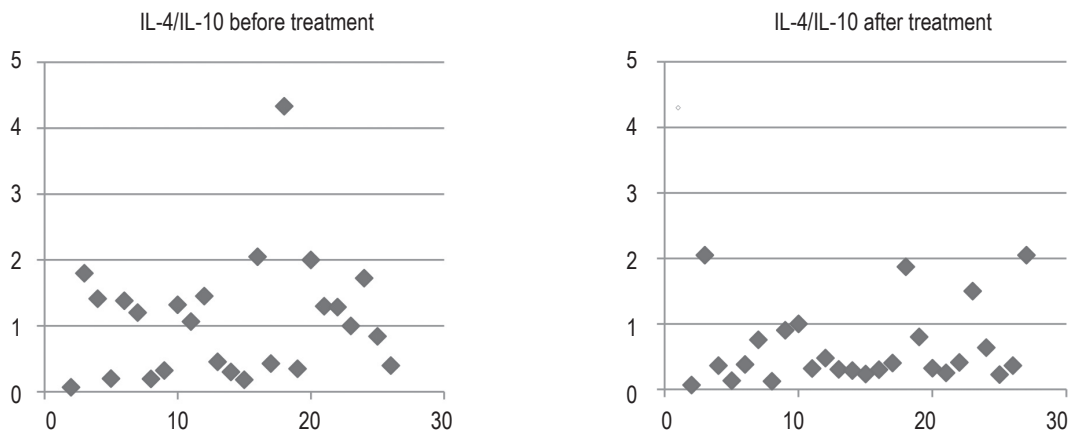


Figure 2. Levels of the IL-4/IL-10 ratio in the study group before and after treatment

However, a number of authors have shown that *Ambrosia artemisiifolia* and *Ambrosia trifida* are not allergenically equivalent species: about 50% of patients receiving specific immunotherapy with one type of ragweed showed little or no clinical response where another species of ragweed prevailed, while the results in these patients were excellent after allergen replacement [1].

To date, the International Union of Immunological Societies (IUIS) has identified 11 allergens of *Ambrosia artemisiifolia*, the main of which are *Amb a 1* and *Amb a 11*. Despite progress in this field, the authors have already paid attention to the fact that at the moment it is impossible to draw a conclusion about the clinical significance of all ragweed allergens, because allergenic activity for the majority of them have not been studied yet [4]. This is important both

for making a correct diagnosis and for improving the effectiveness of treatment.

It is known that ASIT is accompanied by decreased IL-4 levels, increased IL-10 and IFN γ concentration, production of specific IgG4, and decreased level of specific IgE. Currently, the search for immunological markers of the effectiveness of ASIT has been continued. A decrease in IL-4 with good results after ASIT has been noted in many studies [10]. An increase in IL-10 was also recorded by some studies [2]. The level of IFN γ may not change after ASIT, although there is evidence of its increase [11]. It was noted that IL-4/IL-10 or IL-4/IFN γ ratios often have better predictive value than isolated cytokine levels [12].

In our study, we observed a significant decrease in the level of IL-4 from 36.19 to 20.19 pg/ml ($W = 277$; $p = 0.002$); the changes in the level of other cytokines

(IL-10; IFN γ) were insignificant ($p > 0.05$), which is consistent with the data from multiple studies.

The IL-4/IL-10 ratio after treatment in the study group decreased significantly from 1.097 to 0.63 ($p = 0.0063$), while in the control group it remained unchanged ($p = 0.2719$).

Some authors point to a noticeable increase in IgG4 level, which is detected as early as within the first 2 months after the onset of ASIT. IgG, due to the competitive binding of IgE to the allergen, can prevent the activation of, basophils, and dendritic cells. IgG can suppress specific T-cell responses. Allergen-specific IgG4 antibodies against IgE persist after discontinuation of treatment and may provide long-term clinical tolerance [6].

At the same time, researchers often note no clear relationship between the concentrations of IgG antibodies and the clinical results of ASIT. And, perhaps, the clinical effect occurs before the noticeable changes in IgG antibodies [7]. We found that in the study group, there was a slight tendency to increased IgG4 *Amb a 1* and IgG4 *Amb trifida* ($p > 0.05$). The

IgE *Amb trifida* level in the study group did not change after treatment ($W = 150$; $p = 0.74$).

Conclusion

ASIT with *Ambrosia artemisiifolia* allergen in patients with sensitization to *Ambrosia trifida* allows to control the course of an allergic disease. The lack of excellent and low number of good ASIT results is likely due to the intraspecific ragweed allergenic properties. To increase the effectiveness of immunotherapy, the treatment of patients with ragweed pollinosis should be carried out by taking into account individual patient IgE profile and type of allergen typical to any geographic region.

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