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Research article

Changes in the levels of immunological markers after treatment in patients with allergic rhinitis

Cambios en los niveles de marcadores inmunológicos después del tratamiento en pacientes con rinitis alérgica

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ABSTRACT

Introduction: Monitoring changes in the levels of immune markers is of great significance in evaluating the effectiveness of treatment in patients with allergic rhinitis.

Objectives: Determine the change in the concentration of immune markers after treatment in patients with allergic rhinitis caused by cotton dust.

Methods: A descriptive, single-group, comparative before and after intervention study on 52 patients with allergic rhinitis caused by cotton dust. Comparison of immunological markers results before and after 36 months of treatment.


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Results: Total IgE concentration after treatment decreased, the median decreased from 1227.756 U/mL to 676.805 UI/mL. Serum levels of IgG, IgG4, and IgG1 in patients after treatment increased compared to before ($p< 0.001$). The cytokines also changed in the direction of no longer responding toward allergy. Median IL-17 decreased from 1.752 mg/dL to 0.417 mg/dL.

Conclusion: In patients with allergic rhinitis after specific sublingual desensitization treatment, IgE levels and cytokines such as IL-6 and IL-17 are significantly reduced and IgG, IgG4 and IgG1 levels are increased after treatment.

Keywords: allergic rhinitis; cotton dust; IgE; IgG; cytokines.

RESUMEN

Introducción: El monitoreo de los cambios en los niveles de marcadores inmunes es de gran importancia para evaluar la efectividad del tratamiento en pacientes con rinitis alérgica.

Objetivos: Determinar el cambio en la concentración de marcadores inmunes después del tratamiento, en pacientes con rinitis alérgica causada por polvo de algodón.

Métodos: Estudio descriptivo, monogrupo, comparativo antes y después de la intervención, en 52 pacientes con rinitis alérgica por polvo de algodón. Se compararon resultados de marcadores inmunológicos antes y después de 36 meses de tratamiento.

Resultados: La concentración de IgE total después del tratamiento disminuyó, la mediana disminuyó de 1227,756 U/mL a 676,805 UI/mL. Los niveles séricos de IgG, IgG4 e IgG1 en pacientes, después del tratamiento, aumentaron ($p< 0,001$). Las citocinas también cambiaron en dirección a ausencia de respuesta a la alergia. La mediana de IL-17 disminuyó de 1,752 mg/dL a 0,417 mg/dL.

Conclusión: En pacientes con rinitis alérgica, después del tratamiento específico de desensibilización sublingual, los niveles de IgE y citocinas como IL-6 e IL-17 se reducen significativamente y los niveles de IgG, IgG4 e IgG1 aumentan.

Palabras clave: rinitis alérgica; polvo de algodón; IgE; IgG; citoquinas.

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INTRODUCTION

Allergic rhinitis (AR) is a common disease affecting all subjects, from children to the elderly. The disease affects 10% to 40% of adults and 2% to 25% of children worldwide.[1] According to one study, AR prevalence in 4 geographic regions: Asia, Europe, America, and Africa, was reported to be 15%-25%. Children, adolescents, and young adults are the groups most affected by AR.[2]

Diagnosis is based on clinical findings, positive skin prick tests, elevated serum IgE levels, and allergen-specific IgE antibodies.[3] The recommended treatment depends on the severity of the disease. In AR treatment methods, specific desensitization treatment (SDT) is a pathogenesis-based treatment with higher efficiency than other treatments. Some advantages of this method are better clinical progress, reduced cost in treatment, and simple, effective, and safe use, especially can be used for adults and children.[4] After treatment, there is often a big change in immune markers.[5] Therefore, monitoring changes in the levels of immune markers is of great significance in assessing the effectiveness of treatment.

Therefore, this study was carried out to determine the change in the concentration of immune markers after treatment in patients with allergic rhinitis caused by cotton dust.

METHODS

Design: a descriptive, single-group, pre- and post-intervention comparative clinical study to evaluate the change in levels of immune markers after 36 months (3 years) of treatment.

Subjects: workers at garment factories Z176 and X20 under the Ministry of National Defense, Vietnam, from November 2021 to August 2022, satisfying the criteria for participating in the study.

Criteria for selection:


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- Workers diagnosed with AR due to cotton dust allergen:
- Consent to participate in the study.
- Eligible for outpatient treatment for a minimum of 3 years.
- Complete research records.
- If the patient was suffering from an acute bacterial infection in the nose and sinuses in AR patients who meet the above selection criteria, the research team will finish the treatment of the superinfection and then continue to take it into the study.
- Patients being treated with drugs: antihistamines, corticosteroids (local or systemic), after stopping treatment for more than 2 weeks, will be selected for the study if they met the other selection criteria.

Sample size: based on the average estimation formula, as follows:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} \times \sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta} \times \sqrt{p_1(1-p_1) + p_2(1-p_2)}\right)^2}{(p_1 - p_2)^2}$$

Where:

n: minimum study sample size.

p_1: percentage of patients with AR due to cotton dust allergen having a positive skin prick test before treatment, the investigation results in the descriptive study were 100%.

p_2: percentage of patients with AR due to cotton dust allergen having positive skin prick test after treatment. According to research by *Thuan HQ*,[6] the percentage of patients with positive skin prick tests after sublingual SDT with house dust mite allergens was 75.56%. Selected p_2 value of 0.76.

$p = (p_1-p_2)/2 = 0.12$

α: the probability of type I error. In this study, chose $\alpha = 0.05$, then $Z_1 - \alpha/2 = 1.96$.

β: the probability of type II error, this study chose β= 0.2, then Z_1- β = 0.842.

According to the above formula, n= 27 patients were calculated. Adjusted for dropout, with a predicted dropout rate of 25%, the minimum number of patients to include in the intervention study was 36. In fact, 52 patients met the full study criteria. Specifically: 39 patients at factory Z176 and 13 patients at factory X20.

Variables: Evaluation of changes in immune markers before and after 36 months of treatment, including IgE levels, IgG levels, IgG4 levels, IgG1 levels, serum cytokines including IL-2, IL-8, IFN-γ, IL-12, IL-6, IL-17.

Data analysis: data were coded and entered, and analyzed using SPSS 22.0 software. The quantitative variables tested for normal distribution, described through mean, standard deviation, maximum and minimum values. For variables with non-normal distribution: describe through median values, min-max, compare medians of 2 independent groups by Mann-Whitney test, of 2 paired groups by Wilcoxon test. Any variable with p< 0.05 was considered to be statistically significant.

Bioethical aspects: The patient's identity is confidential, and only used for analysis as a group.

RESULTS

Serum IgE concentration in patients after treatment decreased statistically significantly with p< 0.001 compared to before treatment (table 1).

Table 1 - Changes in serum IgE levels before and after treatment (unit: UI/mL)

Time	Indexes				
	n= 52	**Min**	**Max**	**Median**	**p***
Before treatment	52	575.424	38 008.333	1227.756	p< 0.001
After treatment	52	177.855	24 762.500	676.805	


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Serum IgG levels in patients after treatment increased statistically significantly with p< 0.001 compared to before treatment (table 2).

Table 2 - Changes in serum IgG levels before and after treatment (unit: mg/dL)

Time	Indexes			
	n	Min	Max	Median
Before treatment	52	501.820	1605.130	1014.711
After treatment	52	889.794	2995.226	1908.468
P	< 0.001			

Serum levels of IgG1, IgG4 in patients after treatment increased statistically significantly with p< 0.001 compared to before treatment (table 3).

Table 3 - Changes in serum IgG4, IgG1 levels before and after treatment (n= 52)

Indexes	IgG1 (mg/dL)		IgG4 (mg/dL)	
	Before treatment	After treatment	Before treatment	After treatment
Min – Max	190,237 – 1039,985	106,287 – 1852,531	4,823 – 362,322	28,472 – 604,536
Median	563,025	1021,885	45,937	94,792
p	< 0,001		< 0,001	

Serum levels of IL-2, IL-8, and IFN-γ of patients after treatment increased more than before treatment. However, the difference was not statistically significant, with p> 0.05. Serum IL-12 and IL-6 levels in patients increased more after treatment. The difference was statistically significant with p< 0.05. The change in patient serum IL-17 levels before and after 3 years of treatment was statistically significant with p< 0.001 (table 4).

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Table 4 - Changes in serum cytokine levels (pg/mL) (n= 43)

Cytokines	Before treatment	After treatment	p
	Median (Min – Max)	Median (Min – Max)	
IL-2	6.980 (3.431 – 35.377)	15.595 (3.431 – 214.221)	> 0.05
IL-6	35.503 (1.348 – 738.550)	23.233 (1.348 – 67.533)	< 0.05
IL-8	33.274 (2.422 – 3465.959)	40.512 (2.422 – 38666.806)	> 0.05
IL-12	1.401 (0.225 – 5.313)	2.201 (0.225 – 26.503)	< 0.001
IL-17	1.752 (0.209 – 15.910)	0.417 (0.209 – 7.970)	< 0.001
IFN-γ	0.886 (0.099 – 3.606)	1.105 (0.099 – 5.010)	> 0.05

DISCUSSION

Change in total IgE concentration

Serum IgE levels in atopic patients (asthma, AR, dermatitis, urticaria, Quincke's edema, drug allergies) are often high, sometimes very high. Accompanied by an increase in the total serum IgE concentration, there is an appropriate amount of allergen-associated IgE. Quantitative results of total and specific IgE antibody levels before and after immunotherapy treatment, are important in evaluating the effectiveness of the treatment method. If the serum IgE level has decreased after the treatment, the applied treatment has been effective.

After 36 months of SDT treatment with cotton dust allergen at the concentration of 300 IR/mL, the serum IgE concentration decreased markedly; the median IgE before treatment was 1227.756 UI/mL, and after treatment was 676.805 UI/mL (table 1). Compared with before treatment, this result had a statistically significant difference (p< 0.001). Some domestic authors also show similar results. Research by *Huynh Quang Thuan*[6] showed that the mean total serum IgE concentration after AR-specific immunotherapy due to house dust mite allergens was 357.21. The lowest value of total serum IgE was 78.1 UI/mL; the highest was 851.3 UI/mL. When analyzing each patient case, was found that before treatment: The lowest value of serum IgE was 575.424 UI/mL, and the highest was 38008.333 UI/mL. While after treatment: The lowest value of serum IgE was 177.855 UI/mL, and the highest was 24762.500 UI/mL.

Although the results of the total IgE concentration after treatment were still high despite the significant reduction in clinical symptoms and a marked decrease in the skin prick test, this is difficult to explain

when compared with the total IgE concentration of normal people. When each specific case was studied, was found that IgE levels before and after treatment were higher in patients with combined allergic disease than those with AR alone. The study results identified a gradual decrease of IgE in AR patients with cotton dust allergen being treated with SDT. This result was consistent with the improvement of the clinical picture and a significant reduction in the degree of skin prick test positivity. Thus, after 3 years of SDT treatment, the patient's blood IgE decreased significantly, indicating the effectiveness of the treatment.

Change in IgG group concentration

The increase in serum IgG levels following SDT has been shown in recent decades to be mainly due to increased IgG4 and IgG1. Many studies have quantified chemical mediators in 2 groups of AR patients, with 1 group being treated with the allergen. The results showed that in the allergen-treated group, there was a marked reduction in the levels of histamine and prostaglandin E2 compared to the group without allergen treatment. Experimental studies have also shown that the enclosing antibody (IgG4), which is formed after treatment with SDT, can reduce inflammatory phenomena in AR.[7]

Other author has also shown that SDT increases serum IgG4 levels (this antibody can compete with IgE at the receptors of mastocytes and basophils) and regulates Th1 and Th2 subgroups, thereby reducing IgE production. The author also confirmed this in the study of *Demšar LA* et al.[8]

In current study, after 36 months of SDT treatment with cotton dust allergen at 300 concentrations of IR/mL, the patient's IgG concentration increased significantly compared to before treatment ($p < 0.001$). At the same time, the levels of IgG1 and IgG4 increased significantly. The concentration of IgG1 after treatment was 1021.885 (106.287 – 1852.531) (mg/dL) higher than 563.025 (190.237 – 1039.985) mg/dL before treatment, with $p < 0.001$.

The concentration of IgG4 after treatment was 94.792 (28.472 – 604.536) (mg/dL), higher than 45.937 (4.823 – 362.322) (mg/dL) before treatment ($p < 0.001$). It has been shown that after SDT treatment with cotton dust allergen, AR patients have increased the number of protective antibodies. *Jutel M.* et al.[9] also recorded similar results. In their 18-month study, *Queirós M.G.* et al.[10] conducted SDT with a control group; the results showed that specific IgE levels decreased, IgG1 and IgG4 increased simultaneously, which is a significant remission of clinical symptoms and skin prick test results. That is


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also the result of the study of *Stylianou E.* et al.[11] when treating SDT patients with AR for 3 years. This showed the effectiveness of current method on patients.

Changes in serum cytokines concentration

Interleukin-17 and Interleukin-6 (IL-17, IL-6)

AR is considered an excellent model for studying allergic inflammation, with findings likely related to lower airway inflammation in allergic asthma. AR is considered a Th2-mediated disease involving IL-4, IL-5, and IL-13 in the pathophysiology. Recently, however, studies have shown that Th17 cells may be involved in the neutrophil infiltration that occurs during the acute phase of an allergic reaction.[12] IL-17 is the main cytokine produced by Th17 cells, with proinflammatory and chemotactic biologic activities. Results from study of *Hofmann MA.* et al.[13] show the correlation between serum IL-17 and clinical symptoms in AR patients. They proposed to apply IL-17 in serum as an indicator of allergy severity. In the study of *Qiu Q.* et al.,[14] it was shown that the concentration of IL-17 in the disease group was higher than that in the control group, and the concentration of IL-17 in the group of patients decreased significantly compared to before treatment. All authors consider IL-17 as a marker to evaluate the effectiveness of immunotherapy. Therefore, in current study, we evaluated IL-17 instead of IL-4, IL-5, and IL-13.

According to the results of table 4, after 3 years of SDT treatment, a positive change was also recorded. Before treatment, the median IL-17 concentration was 1.752 (0.209 – 15.910) (pg/mL); after treatment, the median IL-17 concentration was 0.417 (0.209 – 7.970) (pg/mL), with significant remission statistically. Thus, current research results are consistent with other authors.[14]

IL-6 is a cytokine that, along with TNF-α and IL-1β, has traditionally been considered more of a biomarker of ongoing inflammation than a regulatory cytokine capable of modulating the immune response. However, recent studies suggest that IL-6 is vital in promoting Th2 differentiation of CD4+ T cells while suppressing Th1 differentiation.[15] IL-6 may also modulate the intensity of the immune response by inhibiting regulatory T cell (Treg) development.[16] More recently, several studies have shown that IL-6 and TGF-β promote the generation of Th17 cells.[17] Many authors have evaluated IL-6 changes before and after AR treatment.[18,19] Current study evaluating IL-6 changes after 3 years of SDT treatment showed reduced IL-6 levels. Before treatment, the median IL-6 concentration was 35.503


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(1.348-738.550) (pg/mL); after treatment, the median IL-6 concentration was 23.233 (1.348-67.533) (pg/mL), a significant reduction statistically. *Barberi S.* et al.[19] also reported a significant reduction in IL-6 after sublingual SDT.[19]

Interferon gamma and interleukin 12 (IFN-γ, IL-12)

The expression of AR results from an interaction between the environment, the immune system, and genetic susceptibility. Several cells, cytokines, and chemokines coordinate and maintain allergic inflammation. Cytokines play an essential role in mediating allergic inflammation. The importance of Th2-cell cytokines in developing allergic sensitization and the pathophysiology of allergic inflammation is well-defined. While healthy subjects were dominated by Th1-type cells, the nasal mucosa and epithelial tissues of AR subjects were dominated by Th2-type lymphocytes.

For Th1, the well-known cytokine, IFN-γ, is a potent and relatively specific inhibitor of IgE and IgG4 synthesis by IL-4-induced B cells. The previous study by *Degirmenci PB.* et al.[14] also showed that serum IFN-γ levels in AR patients were detected at a lower level than in controls, and an inverse relationship between symptom scores and concentrations of this cytokine.[20]

Meanwhile, IL-12 is produced by B cells, macrophages, and dendritic cells and mainly regulates Th1 cell differentiation while suppressing the expansion of Th2 cell lines. These cytokines are involved in the pathogenesis of allergic diseases. In this context, the production of IL-12 and IFN-γ in asthma was found to be decreased. Together with IL-18, IL-12 induces anti-CD40-activated B cells to induce IFN-γ, which inhibits IL-4-dependent IgE production.[21]

In this study, the change in IFN-γ and IL-12 levels after 3 years of treatment was evaluated. The study results showed that the median concentration of IFN-γ and IL-12 before treatment was 0.886 (0.099 - 3.606) and 1.401 (0.225 - 5.313) (pg/mL), respectively. These concentrations after treatment were 1.105 (0.099-5.010) and 2.201 (0.225 - 26.503), respectively (pg/mL). The change of these values before and after treatment is consistent with the review study of other authors.[22] The increase in serum IL-12 and IFN-γ and the improvement in the patient's nasal symptoms after treatment suggest that the treatment is effective.

Overall, the increase in IgG, and IgG4 levels, the decrease in total IgE levels, and the positive change in cytokines after treatment demonstrated an altered immune response, expressed by localization of the

immune system. Skin prick tests were significantly reduced in positivity. All these changes are consistent with clinical improvement after treatment. These results demonstrate an effective treatment, similar to the conclusions of *Liu X*. et al.[23] when reviewing several efficacy studies of sublingual specific immunity in Asia.

In conclusion, patients with allergic rhinitis after specific sublingual desensitization treatment, the levels of IgE and cytokines such as IL-6 and IL-17 were significantly reduced, and the levels of IgG, IgG4, and IgG1 were increased after treatment.

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Conflict of interest

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