NCJSC «Karaganda Medical University»

**ANNOTATION**

dissertation work for the degree of Doctor of Philosophy

Topic: «Biomarkers of the effectiveness of allergen-specific immunotherapy in patients with seasonal allergic diseases»

Specialty: 6D 110100 «Medicine»

Performed by: doctoral student Izmailovich Marina

Supervisor: Doctor of Medical Sciences,

Professor, Vice-Rector for Clinical Work

Astana Medical University Gazaliyeva Meruyert

Scientific consultant: Ph.D., M.D., Associate

Professor, Department of Epidemiology,

Biostatistics and Evidence Based Medicine,

Al-Farabi Kazakh National University Glushkova Natalya

Foreign scientific consultant: Professor,

Dean of the School of Medicine and Health Science

BAU Batumi International University Akhvlediani Leila

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**Relevance**

Currently, seasonal allergic diseases are recognized as a significant medical and social problem worldwide [1]. According to data from the World Health Organization (WHO), approximately 40% of the global population suffers from allergies [2-4], with a persistent increase in morbidity and an expansion in the spectrum of sensitization to unrelated allergens, leading to more severe forms [5,6]. Among these diseases, seasonal allergic rhinitis (AR) has emerged as a challenging situation [4], affecting over 500 million people worldwide [7-10]. In Europe, AR affects 23-30% of the population, while in the United States of America, it affects 12-30% of the population, and in Russia, it affects 17-35% of adults [11-16]. Furthermore, allergic reactions to plant-based foods are detected in 40-70% of cases, including those not related to cross-allergens, significantly complicating diagnostic orientation [17]. In the Republic of Kazakhstan, the prevalence of allergic rhinitis is 15-20% among urban residents and 10-15% among rural residents [18], and all of these figures are increasing according to global trends [19].

Pollinosis is the most prevalent seasonal allergic disease in Kazakhstan, affecting one in four individuals worldwide [20]. The most frequent clinical manifestation of pollinosis is seasonal allergic rhinitis, characterized by rhinorrhea, nasal congestion, nasal itching, and sneezing, which are reversible after the cessation of allergen exposure or during treatment [21-23]. In recent decades, seasonal allergic rhinitis has become a significant problem for Kazakhstan, with various factors, including climatic and geographical conditions, the ecological situation, and the level of socio-economic development of the region, exacerbating morbidity [18,19]. In recent years, the link between allergic diseases and low vitamin D content has been studied worldwide, and a correlation has been established between low levels of vitamin D in blood serum and an increased prevalence of immune disorders [24]. These characteristics, coupled with the low-income population's low levels of vitamin D, have led to an exacerbation of respiratory allergic diseases [25].

Currently, allergen-specific immunotherapy (ASIT) is considered the primary pathogenetic method for treating seasonal allergic diseases, and it has been supported by several studies [6, 7, 8]. ASIT is capable of influencing all pathogenetic mechanisms underlying the allergic process, providing long-term preventive effects and persistent remission after treatment completion [26]. Recent researches on ASIT have proposed vitamin D as a potential factor that can affect the therapy's outcome [9]. Therefore, vitamin D insufficiency could be a potential determinant of ASIT efficacy, and its supplementation could improve treatment outcomes [10]. However, the current data on the interaction between vitamin D and the response to ASIT remains contradictory and insufficiently studied.

Incorporating the pathogenetic mechanism of ASIT, the study suggested using general and specific immunoglobulin E and eosinophilic cationic protein as biomarkers of the therapy's effectiveness [11, 12, 13]. Molecular allergodiagnostics (MA) is currently the most reliable method for the differential diagnosis of true sensitization and cross-reactivity in polysensitized patients, which allows the selection of an appropriate ASIT drug [4]. This diagnostic approach can simultaneously detect allergen-specific immunoglobulin E to over one hundred recombinant allergenic molecules, which significantly assists in determining the causally significant allergen for ASIT selection [5].

Considering the aforementioned challenges in treating seasonal allergic rhinitis, it is crucial to find a personalized approach for developing an optimal ASIT protocol. Addressing this issue could positively impact the quality of life of patients who require ASIT.

**The working hypothesis -** The addition of hydroxyvitamin D (25 OH D) to the treatment protocol of allergen-specific immunotherapy has been demonstrated to enhance the therapeutic efficacy in patients with seasonal allergic diseases, such as seasonal allergic rhinitis.

**The aim of the study -** The refinement of the algorithm for allergen-specific immunotherapy in the management of seasonal allergic diseases, with particular focus on the context of seasonal allergic rhinitis.

**Research objectives**

1. To perform a comprehensive systematic review of relevant literature on allergen-specific immunotherapy.
2. To investigate the clinical and laboratory efficacy of various allergen-specific immunotherapy protocols, through a randomized clinical trial.
3. To determine prognostically significant laboratory markers of the effectiveness of allergen-specific immunotherapy in combination with vitamin D.
4. To establish a clinical and diagnostic algorithm that can be applied in the management of patients with seasonal allergic diseases, with specific emphasis on seasonal allergic rhinitis.

**Scientific novelty**

A systematic review was conducted for the period from 2011 to 2021, employing a strict methodological approach. The collected data unequivocally supports the enhanced effectiveness of Adapted Allergen-Specific Immunotherapy (ASIT) in patients with an established causally significant allergen after implementing the Modified Allergen Delivery (MAD) technique.

A comprehensive comparative evaluation encompassing clinical parameters (overall symptom assessment, pharmacotherapy necessity, and quality of life evaluation) as well as laboratory markers (total immunoglobulin E (IGE), eosinophilic cationic protein (ECB), allergen-specific IGE, and serum vitamin D levels) was undertaken. This assessment examined the impact of combining ASIT with vitamin D in patients suffering from seasonal allergic rhinitis, both before treatment, after treatment, and during the allergen-induced dusting season.

From a molecular allergodiagnostics perspective, the algorithm for allergen-specific immunotherapy in seasonal allergic diseases was optimized for the first time. A personalized approach to the administration of ASIT was introduced, leading to improved treatment strategies for patients with allergic rhinitis based on the findings of this study.

Groundbreaking results were obtained for the first time in the Republic of Kazakhstan, demonstrating that total IGE levels and blood vitamin D levels serve as the most significant prognostic markers of the effectiveness of allergen-specific immunotherapy when combined with vitamin D.

Unprecedented research conducted in the Republic of Kazakhstan focused on the investigation of the quality of life in patients receiving ASIT combined with vitamin D.

**The main provisions for defense**

1. Molecular allergodiagnostics represents a highly precise approach for the selection of an allergenic profile in allergen-specific immunotherapy. This method enables the identification of predictive factors for the efficacy of allergen-specific immunotherapy.
2. The combination of ASIT and vitamin D offers a superior therapeutic option when compared to the classical ASIT scheme. This superiority is clinically confirmed by reduced severity of symptoms and higher quality of life scores, as well as laboratory evidence of decreased general and specific immunoglobulin E levels, eosinophilic cationic protein levels, and elevated vitamin D levels in the bloodstream.
3. The most significant prognostic markers for evaluating the effectiveness of allergen-specific immunotherapy in conjunction with vitamin D are the vitamin D level and total immunoglobulin E.
4. The developed and proposed clinical diagnostic algorithm for the management of seasonal allergic rhinitis is an effective tool that improves the quality of life and reduces the severity of symptoms in patients in practice.

**Theoretical significance**

The research conducted in this dissertation significantly contributes to the current understanding of the diagnosis and treatment of seasonal allergic rhinitis for allergologists and immunologists.

As a result of the dissertation research, methodological recommendations titled "Assessment of patients' condition with seasonal allergic rhinitis during allergen-specific immunotherapy" have been formulated. These recommendations not only expand the theoretical knowledge of medical practitioners but also translate into practical implementation by allergologists and immunologists at outpatient facilities. The implementation of these recommendations has been initiated at KGP "Polyclinic No. 1 of the city of Karaganda," KGP "Polyclinic No. 3 of the city of Karaganda," KGP "Polyclinic No. 4 of the city of Karaganda," and KGP "Polyclinic No. 5 of the city of Karaganda" (Appendix A and B).

Furthermore, the methodological recommendations titled "Assessment of patients' condition with seasonal allergic rhinitis during allergen-specific immunotherapy" have been incorporated into the training programs of interns, residents, and allergologists-immunologists at the Department of Internal Diseases of the NCJSC "MUK" (Appendix A and B).

**Practical significance**

Valuable contributions have been made to the field of allergology and immunology with the development of an effective tool for evaluating symptom severity and quality of life in patients suffering from seasonal allergic rhinitis. This tool has been successfully integrated into the operational procedures of medical organizations, as evidenced by Copyright Certificate No. 14535 issued on 19.01.2021. Implementation of this tool has been observed at KGP "Polyclinic No. 1 of the city of Karaganda" and KGP "Polyclinic No. 5 of the city of Karaganda" (see Appendix B).

In addition, a comprehensive scheme combining allergen-specific immunotherapy with vitamin D for the treatment of seasonal allergic rhinitis has been meticulously developed and put into practice by allergologists and immunologists. The author's certificate, issued on 29.01.2021 (Registration No. 14750), confirms the originality and significance of this scheme. Acts of implementation at KGP "Polyclinic No. 1 of the city of Karaganda" and KGP "Polyclinic No. 5 of the city of Karaganda" validate its practical application (see Appendix B).

Furthermore, an algorithm for managing seasonal allergic rhinitis in outpatient settings has been devised exclusively for allergologists and immunologists. This algorithm has been effectively implemented in medical organizations, supported by Copyright Certificate No. 14774, issued on 01.02.2021. Acts of implementation at KGP "Polyclinic No. 1 of the city of Karaganda" and KGP "Polyclinic No. 5 of the city of Karaganda" further substantiate its practical utilization (Appendix B).

**Author's personal contribution**

The study was conducted independently, including the recruitment of participants, primary and statistical data processing, analysis, and generalization of research findings. All chapters of the dissertation were written, and the researcher participated in conferences, obtained author's certificates, acts of implementation, and worked with publications from drafting the material to submission to scientific journals.

**Approbation of work**

The key findings of the dissertation were presented and deliberated at multiple events, including the 62nd scientific and practical student conference with international participation "Student Science and Health" held by NCJSC "Semey Medical University" on May 15, 2020 in Semey, the 8th International Conference on Research in Life-Sciences & Healthcare (ICRLSH) in Singapore on June 26-27, 2021, and an extended meeting of the Department of Internal Diseases of NCJSC "Medical University of Karaganda".

**Publications**

Based on the findings of the dissertation, a total of 14 scientific papers have been published. Among them are four articles in scientific publications recommended by the Committee for Control in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, two articles in international scientific publications included in the Scopus information base at the time of publication (in the journals "Cells" and "Russian Open Medical Journal"), one article in international scientific publications indexed in the RSCI and included in the HAC list, and three publications in the materials of international conferences. Additionally, three certificates of entry of information into the state register of rights to objects protected by copyright have been obtained. Furthermore, methodological recommendations have been developed for doctors, authored by Izmailovich M. R., Gazaliyeva M. A., and Glushkova N. E. These recommendations focus on the assessment of the condition of patients with seasonal allergic rhinitis who receive allergen-specific immunotherapy.

**The structure and scope of the dissertation**

The dissertation comprises 126 pages of typed text, featuring 20 tables and 12 figures. It is divided into several sections, including an introduction, a literature review, a materials and methods section, results of original research, a discussion of the findings, a conclusion, normative references, designations and abbreviations, references, and appendices. The bibliography includes a total of 180 sources in both Russian and English.

**Materials and research methods**

The research on the topic of the dissertation was conducted in the period from June 1, 2020 to August 31, 2021 on the basis of the Regional Allergological Center "DiVera".

During the research work, clinical and laboratory changes in allergen-specific immunotherapy were studied in patients with seasonal allergic rhinitis in combination with vitamin D.

In total, 55 male and female patients aged 18 to 60 years participated in the study.

There were 3 main stages in the structure of the study:

Stage 1 of the study: a systematic review of studies on allergen-specific immunotherapy.

Design: a systematic review.

Stage 2 of the study: randomized clinical trial (group 1: adapted allergen-specific immunotherapy scheme in combination with hydroxyvitamin D (25OND) and group 2: classical allergen-specific immunotherapy scheme) of a random sample of 55 patients with seasonal allergic rhinitis. During the implementation of this stage, we identified the main clinical and laboratory markers of the effectiveness of allergen-specific immunotherapy, which have the greatest prognostic significance.

Design: randomized clinical trial.

Stage 3 of the study is presented by conducting an analytical study in order to create a clinical diagnostic algorithm for the diagnosis and treatment of seasonal allergic rhinitis for subsequent improvement of clinical management of seasonal allergic rhinitis.

Design: analytical research.

**Study design**

In the initial phase of our research, a systematic review of studies related to allergen-specific immunotherapy was performed. A comprehensive literature search was conducted using the electronic databases PubMed, Google Scholar, and e-library. The search was conducted with the help of relevant keywords such as allergen-specific immunotherapy, eosinophilic cationic protein, total immunoglobulin E, and molecular allergodiagnostics. The search spanned a period of 14 years, from January 1, 2008, to December 31, 2021. Only those research papers that provided a comprehensive insight into the problem were selected for the review.

In the subsequent stage of our work, we conducted a randomized controlled clinical trial, as depicted in Figure 1.



Figure 1 – Characteristics of control points of a randomized clinical trial

All patients that were part of the study underwent a thorough consultation with an allergist to evaluate their clinical status and undergo laboratory examinations. Objective evaluation of clinical condition was performed, along with a questionnaire to determine the severity of seasonal allergic rhinitis symptoms and the impact of the disease on the patient's quality of life. An adapted questionnaire for assessing seasonal allergic rhinitis symptoms and quality of life (Copyright Certificate No. 14535 of 19.01.2021) was used for this purpose. Laboratory examination included the determination of total immunoglobulin E, eosinophilic cationic protein, vitamin D, and specific immunoglobulin E through the ISAC test. To assess the dynamic changes of immunological parameters during allergen-specific immunotherapy in patients with seasonal allergic rhinitis, specific immunoglobulin E to recombinant allergens, total immunoglobulin E, eosinophilic cationic protein, and vitamin D (25OHD) were monitored.

**Phases of the study:**

Phase I: In the first phase, all patients underwent a clinical assessment and laboratory examination, including a questionnaire to evaluate the severity of clinical symptoms and quality of life (methodology in section 2.1.3). The laboratory examination involved the determination of serum levels of eosinophilic cationic protein, specific immunoglobulin E (ISAC test), vitamin D, and total immunoglobulin E [27]. The patients were then divided into two groups, with one receiving the drug Antipollin according to the classical scheme, and the other group receiving it according to an adapted scheme in combination with vitamin D.

Phase II: The second phase took place after 2.5 months or 10 weeks, when patients from both groups came to the doctor for an examination, laboratory testing to determine serum levels of eosinophilic cationic protein, specific immunoglobulin E (ISAC test), vitamin D, and total immunoglobulin E, outside the exacerbation season.

Phase III: The third phase was conducted after 8 months or 32 weeks when patients from both groups came to the doctor for an examination, anamnesis collection, and a questionnaire to determine the severity of exacerbation symptoms and quality of life during the exacerbation season. The control point involved a repeated examination of the patient and registration of the results. Patients who missed the control point were automatically excluded from the study. If signs of exacerbation appeared, patients were advised to discontinue the drug and use antihistamines for 3 days, after which treatment continued.

**Intervention Characteristics:**

Allergen-specific immunotherapy was carried out with the drug "Antipollin" in the form of tablet sublingual extracts of allergens of the company "Burli" according to the scheme attached to the manufacturer's instructions. The drug is allowed for use on the territory of the Republic of Kazakhstan on the basis of the order of the Chairman of the CCMFD of the Ministry of Health of the Republic of Kazakhstan dated November 6, 2012 No. 845 [28].

Antipollin is a standardized complex consisting of three components. The first is a standardized extract from plant pollen (one, two or three allergens). Its volume is 15% of the tablet weight. The second is ascorbic acid in a dose of 0.05 g – 15% of the tablet weight; the third is a carrier for creating a solid, easily soluble tablet in the mouth with a percentage of excipients of 70%. The range of Antipollin tablets is about 20 types, including various mixes. We used the compositions " Antipollin mixed wormwood", "Antipollin timothy grass", " Antipollin birch", "Antipollin weed mix".

Treatment is prescribed to each patient by an allergist during the period of complete remission and at least 2 months before the onset of flowering of the causal allergen. The tablet is placed behind the cheek or under the tongue and held until completely dissolved, without drinking water. Apply the drug on an empty stomach at the same time. The first intake of the drug is carried out in the presence of the attending physician, then the patient independently took the drug according to a certain scheme with control visits to the attending physician.

Allergen-specific immunotherapy was carried out according to the standard scheme in 3 stages [28]: stage 1 – the initial course, during which the dose was increased with a constant increase in the concentration of the allergen for 1 month, starting with a dose of 0.0001 PNU to reach 1 PNU; stage 2 – the main course, for 26 days the concentration increase continues allergen from 10 to reach the maximum permissible dose of 1000 PNU; stage 3 - maintenance course, consists in applying the maximum permissible dose and concentration of allergen in 1000 PNU, one tablet 1 time after 2 days for 16 days. The treatment was completed 2 weeks before the expected flowering season of plants with increased sensitivity to pollen.

The classical scheme of sublingual allergen-specific immunotherapy was assigned to the control group. The intervention group was assigned an adapted allergen-specific immunotherapy regimen in combination with vitamin D for two and a half months. The selection of the dose of vitamin D in the intervention group (ASIT + vitamin D) was carried out according to the scheme, in accordance with the level of deficiency in the patient's blood serum to achieve the expected level of 40 ng/ml.

**Statistical research methods**

The statistical analyses were performed using "Statistica for Windows v. 13.0" software (StatSoftInc, USA) and online programs https://stattech.ru/databases. Descriptive statistics were used to analyze the data. The normality of the distribution of variables was assessed using the Shapiro-Fork test, Kurtosis coefficient, and Kolmogorov-Smirnov criterion. A critical significance level of p < 0.05 was used to reject the null hypothesis of normality. For normally distributed quantitative variables, the mean and standard deviation were calculated. For non-normally distributed variables, the median, 25%, and 75% quartiles were calculated.

Frequency tables were used to determine the occurrence of values for qualitative variables. Categorical data were presented as absolute numbers and percentages of the entire group. The Chi-square criterion was used to compare the frequency of distribution of patients by qualitative characteristics between groups, and a p < 0.05 was used to reject the null hypothesis of frequency differences within the groups.

The Mann-Whitney criterion was used to compare parameters expressed in quantitative variables between groups. The Chi-square criterion was used to compare parameters expressed in qualitative variables between groups. The Wilcoxon criterion was used to find differences in two related (dependent) groups. McNemar's criteria were used to compare qualitative data that were dependent for two observation points.

Correlation analysis was performed to determine the linear relationships between quantitative and binary qualitative variables. The correlation analysis was conducted using Spearman's statistical correlation criterion. Multivariate logistic regression was used to find dependencies between the outcome and various indicators and to determine the predictor variables. A p < 0.05 was used to reject the null hypothesis of no dependence between the predictor and the outcome. A predictor with an Expß value of more than 1.0 was considered to have an impact on the outcome, and the quantitative value was further interpreted.

**Conclusions**

1. The systematic review conducted on the utilization of molecular diagnostics in allergen-specific immunotherapy has revealed its pivotal role in the selection of the allergenic composition for ASIT. Furthermore, it exerts a significant influence on the effectiveness and outcomes of ASIT.
2. Clinical and laboratory evidence confirms that the ASIT scheme combined with vitamin D exhibits superior efficacy compared to the standard protocol. In the ASIT + vitamin D group, notable improvements were observed in various parameters. Specifically, the overall severity score of symptoms exhibited a more pronounced decrease compared to the ASIT group (6 points vs. 9 points, respectively; p<0.04). The total quality of life score also displayed significant enhancement (7 points vs. 9.5 points, respectively; p<0.001). Additionally, the levels of eosinophilic cationic protein (ECB) showed a notable reduction in the ASIT + vitamin D group compared to the ASIT group (32.61 ng/ml vs. 40.28 ng/ml, respectively; p<0.001). The total immunoglobulin E (IGE) levels were also significantly lower in the ASIT + vitamin D group (209.6 units/ml) compared to the ASIT group (299.75 units/ml; p<0.01). Moreover, the concentration of vitamin D in the blood serum after therapy was significantly higher in the ASIT + vitamin D group (37.6 ng/ml) compared to the ASIT group (13.4 ng/ml; p<0.001), effectively reaching reference norms during the course of therapy.
3. The most significant laboratory markers for assessing the efficacy of ASIT with vitamin D are the total IGE level and the concentration of vitamin D in the blood serum. Threshold values have been identified, indicating the predictive significance of total IGE and vitamin D concentrations in relation to the severity of symptoms in seasonal allergic rhinitis. A higher total IGE level and lower vitamin D concentration are associated with more severe symptoms. Total IGE levels below 368,7 IU/ml and vitamin D levels above 18,6 ng/ml suggest a stable disease course but warrant consideration as a risk group. Correlation analysis of laboratory markers of the effectiveness of ASIT in combination with vitamin D showed that the severity of symptoms of allergic rhinitis increases with a decrease in the basic level of vitamin D (r=-0.8; p=0.00000), with an increase in the indicators of total immunoglobulin E (r=0.9; p=0.00000), eosinophilic cationic protein (r=0.8; p<0.001) and specific immunoglobulin E to the components of the allergen Timothy sIgE rPhlp1 (R=0.7; p<0.0008), sIgE rPhlp 5 (R=0.7; p=0.1428), Birch sIgE rBet v1 (R=0.7; p=0.1866), Wormwood sIgE nArt v1 (R=0.7; p<0.00001).
4. The developed clinical and diagnostic algorithm for managing seasonal allergic rhinitis has effectively demonstrated the positive impact of introducing allergen-specific immunotherapy combined with vitamin D. Clinical improvements were observed, with the average severity of symptoms decreasing from 11 to 6 points (p<0.001) ; and based on laboratory biomarkers, the total IGE was reduced from 387.2 units/ml up to 209.6 units/ml (p<0.005), the vitamin D level showed an increase from 16.32 ng/ml to 37.6 ng/l (p<0.001).

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