BIOSCIENCE JOURNAL

EFFECT OF MITE-SPECIFIC SUBCUTANEOUS IMMUNOTHERAPY ON PATIENTS WITH ALLERGIC RHINITIS

Guoyan SUN[1], Shuangba HE[1], Qingxiang ZHANG[1]

[1]Nanjing Tongren Hospital, Nanjing 211100, Jiangsu Province, China.

Corresponding author:
Shuangba He
hesbnth@uic-edu.cn
Qingxiang Zhang
zhangqx@njtrh.org

How to cite: SUN, G., HE, S. and ZHANG, Q. Effect of mite-specific subcutaneous immunotherapy on patients with allergic rhinitis. *Bioscience Journal*. 2024, **40**, e40041. https://doi.org/10.14393/BJ-v40n0a2024-70819

Abstract

This study analyzed the effect of mite-specific subcutaneous immunotherapy (SCIT) on patients with allergic rhinitis (AR). We enrolled 98 AR patients visiting our hospital from April 2017 to April 2019 and grouped them in a random number table. The control group (n=49) received conventional treatment for three years. The SCIT used a standardized mite allergen injection for the experimental group (n=49) for three years. The study compared total nasal symptom score (TNSS), daily medication score (DMS), total combined score (TCS), visual analog scale (VAS) score, mini-rhinitis quality of life questionnaire (MiniRQLQ) score, and serum immunoglobulin E (sIgE) level before and after treatment. The overall response rate was higher in the experimental group than in the control group (59.18% *vs*. 30.61%, $p<0.05$). After treatment, the experimental group had lower values for TCS and VAS score ($p<0.05$); motion score; practical problems; nasal, ocular, and other symptoms ($p<0.05$); and sIgE, *Dermatophagoides pteronyssinus* (Dp)-sIgE, and *Dermatophagoides farinae* (Df)-sIgE levels ($p<0.05$) than the control group. The sIgE, Dp-sIgE, and Df-sIgE levels were lower in the effective group than in the ineffective group ($p<0.05$). The areas under the ROC curves of IgE, Dp-sIgE, and Df-sIgE and their combination for predicting the therapeutic effect of mite-specific SCIT on AR were 0.839, 0.779, 0.814, and 0.903, respectively. Mite-specific SCIT relieved clinical symptoms and improved the quality of life of AR patients, probably by decreasing the IgE expression level.

Keywords: Allergic rhinitis. Immunoglobulin E. Mite. Subcutaneous immunotherapy.

1. Introduction

Allergic rhinitis (AR), also named anaphylactic rhinitis, is a non-infectious inflammatory disease of the nasal mucosa. It mainly occurs due to the joint involvement of immunologically competent cells and cytokines in the body, mediated by immunoglobulin E (IgE), after the exposure of susceptible individuals to allergens (Bousquet et al. 2020). According to epidemiological statistical analyses, AR incidence is as high as 3.3-37.9% in the pediatric population. This incidence reaches 80% in asthma patients, and as much as 40% of AR patients have asthma (Alvaro et al. 2020). Clinically, AR is primarily characterized by symptoms such as episodic sneezing, runny nose, and nasal obstruction, accompanied by lower respiratory tract symptoms, including chest distress and asthma, as the disease progresses. Despite the low mortality rate, AR increases the economic burden on families and society and may affect patients' regular work activities and sleep (Boonpiyathad et al. 2019; Aun et al. 2020).

Dermatophagoides pteronyssinus (Dp) allergy is the main predisposing factor of AR (Wang et al.

2022), potentially accompanied by other allergic diseases, such as conjunctivitis and asthma, during AR progression. Diseases induced by allergy to dust mites are mainly perennial, and specific antibodies in nasal mucosal surface secretions may block or neutralize antigens before they bind to IgE in mast cells and basophils. Hence, IgE levels may be highly significant for disease development and progression. Today, subcutaneous immunotherapy (SCIT) is the primary AR treatment. SCIT induces immune tolerance by the local incremental subcutaneous injection of allergens from low to high doses and is the only clinically recognized treatment method for diagnosing the cause of the disease (Shamji et al. 2022). SCIT is extensively applied to treat nasal symptoms in AR patients, relieving clinical symptoms, thereby improving the quality of life, preventing allergen formation, reducing the incidence of AR progressing to asthma, and controlling its evolution (Hamed et al. 2019). It is an effective treatment method for AR remission in clinical practice. Therefore, this study assessed the therapeutic effect of mite-specific SCIT on AR patients to provide valuable evidence for future treatments.

2. Material and Methods

General data

The study selected 98 AR patients treated in our hospital from April 2017 to April 2019 and grouped them in a random number table. There were 55 men, and 43 women aged eight to 57 years, and the average age was (31.61±3.62). The disease course was one to five years, with (2.64±0.42) years on average. The hospital's Medical Ethics Committee approved this study.

Inclusion and exclusion criteria

The inclusion criteria were 1) patients meeting the diagnostic criteria for AR (8), namely patients (i) with two or more main manifestations of sneezing, watery nasal discharge, itchy nose, and nasal obstruction lasting for >1 hour or a cumulative of >1 hour, possibly accompanied by ocular symptoms such as lacrimation, eye redness, and itchy eyes, (ii) with clinical signs, such as pale and edematous nasal mucosa and watery nasal discharge, and (iii) testing positive in at least one allergen skin prick test (SPT) and/or serum-specific IgE; 2) AR patients with asthma and well-controlled asthma symptoms; and 3) patients who signed the informed consent.

The exclusion criteria were patients 1) allergic to the drugs used in this study; 2) with severe or uncontrolled asthma and/or irreversible airway obstructive disease; 3) recently treated with β-receptor blockers or angiotensin-converting enzyme inhibitors (ACEI); 4) with cardiovascular, immune, neurological, gastrointestinal, or hematological disorders; or 5) pregnant or lactating women.

Methods for the control group

Glucocorticoids, antihistamines, antileukotrienes, mast cell membrane stabilizers, decongestants, and anticholinergics were administered according to the therapeutic regimen recommended in the literature (Cheng et al. 2018).

Methods for the experimental group

The Dp allergen preparation (ALK-Abello A/S, approval N.: S20090048) was used for two treatment stages: initiation (dose escalation stage) and maintenance (dose maintenance stage). The preparation was injected subcutaneously once a week at the distal 1/3 of the upper arm of patients in the initiation stage, with an initial dose of 20 SQ-U and increasing doses of 20, 40, 80, 200, 400, 800, 2000, 4000, 8000, 10,000, 20,000, 40,000, 60,000, 80,000, and 100,000 SQ-U, for 15 weeks. Maintenance treatment started at week 17 by injecting the preparation at 100,000 SQ-U (1 mL) once in week 17, four weeks later, and every six weeks until the end of the treatment course, which lasted for three years.

Observation of indicators

(1) Efficacy evaluation was based on subjective feelings before treatment and after three years and classified into markedly effective (disappearance of symptoms in the maintenance stage), effective (effective improvement of clinical symptoms in the maintenance stage), and ineffective (no improvement or even aggravation of clinical symptoms in the maintenance stage). Overall response rate = (markedly effective + effective)/n ×100.00%.

(2) The patients received scales for total nasal symptom score (TNSS), daily medication score (DMS), and total combined score (TCS) before treatment and after three years. The TNSS scale consisted of four nasal symptoms (nasal obstruction, runny nose, itchy nose, and sneezing), with 0-3 points for each symptom: zero points for no symptoms, one point for mild symptoms, two points for moderate symptoms, and three points for severe symptoms. The total TNSS scale was 0-12 points, with higher scores indicating higher symptom severity. As for the DMS scale, one, two, and three points represented antihistamines, nasal glucocorticoids, and oral glucocorticoids, respectively. The TCS was the sum of TNSS/number of symptoms and DMS. Clinical signs and symptoms were scored with a 10-cm straight line using the visual analog scale (VAS) score, with zero points for no symptom effects and ten points for intolerable symptom effects.

(3) The mini-rhinitis quality of life questionnaire (miniRQLQ) assessed the quality of life with five items and a 0-6-point score: motion, practical problems, and nasal, ocular, and other symptoms. Higher scores indicated lower quality of life and higher impact.

(4) The serum IgE (sIgE) level was measured. Specifically, 5 mL of fasting venous blood was collected before treatment and, after three years, centrifuged and subjected to enzyme-linked immunosorbent assay (ELISA) to detect sIgE and Dp- and *Dermatophagoides farinae* (Df)-sIgE levels. Patients were grouped according to the response rate, and sIgE levels were compared between the two groups. Also, receiver operating characteristic (ROC) curves were plotted to analyze pre-treatment IgE values for predicting efficacy.

Statistical analysis

SPSS 25.0 software processed all data. The measurement values were expressed as (`x ± s) and compared between groups by the independent-samples t-test and within groups with the paired-samples t-test. The counts were expressed as a ratio (%) and subjected to the χ2 test. The plotted ROC curves analyzed the predictive values of sIgE, Dp-sIgE, and Df-sIgE. The $\alpha=0.05$ and $p<0.05$ calibration levels suggested a statistically significant difference.

3. Results

General data

Sex, age, and disease course did not show statistically significant differences between experimental and control groups ($p>0.05$) (Table 1).

Table 1. General data [n, ($\bar{x}$ ± s)].

Group	n	Male/female	Age (year)	Course of disease (year)
Control	49	30/19	31.78±2.44	2.63±0.24
Experimental	49	25/24	31.63±2.57	2.65±0.25
χ^2/t		1.036	0.296	0.404
P		0.309	0.768	0.687

Treatment outcomes

The total response rate was higher in the experimental group (59.18%) than in the control group (30.61%) ($p<0.05$) (Table 2).

Table 2. Treatment outcomes [n (%)].

Group	n	Markedly effective	Effective	Ineffective	Total response rate
Control	49	3 (6.12)	12 (24.49)	34 (69.39)	15 (30.61)
Experimental	49	6 (12.24)	23 (46.94)	20 (40.82)	29 (59.18)
χ^2					8.084
P					0.004

TCS and VAS score

TCS and VAS score did not present statistically significant differences between experimental and control groups before treatment ($p>0.05$). After treatment, TCS and VAS score were lower in the experimental group than in the control group ($p<0.05$) (Table 3).

Table 3. TCS and VAS score before and after treatment [($\bar{x} \pm s$), point].

Group	n	TCS		VAS score	
		Before treatment	After treatment	Before treatment	After treatment
Control	49	13.24±2.47	5.28±0.79	7.08±2.15	3.45±1.28
Experimental	49	13.65±2.51	1.64±0.82	7.14±2.10	1.76±0.89
t		0.815	22.378	0.140	7.588
P		0.417	<0.001	0.889	<0.001

*p<0.05 *vs*. before treatment within the group.

MiniRQLQ scores

The scores of motion, practical problems, and nasal, ocular, and other symptoms in the experimental group did not show statistically significant differences compared with those in the control group before treatment ($p>0.05$). After treatment, these scores were lower in the experimental group than in the control group ($p<0.05$) (Table 4).

Table 4. MiniRQLQ scores before and after treatment [($\bar{x} \pm s$), point].

Group	n	Motion		Practical problems		Nasal symptoms		Ocular symptoms		Other symptoms	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	49	3.47±1.25	2.65±0.58*	3.41±1.15	2.74±0.53*	3.34±1.20	2.67±0.52*	3.31±1.02	2.54±0.61*	3.49±1.20	2.07±0.34*
Experimental	49	3.12±1.18	1.94±0.53*	3.45±1.18	1.92±0.48*	3.26±1.23	1.98±0.50*	3.25±1.08	1.83±0.46*	3.55±1.24	1.35±0.28*
t		1.425	6.326	0.170	8.027	0.326	6.695	0.283	6.505	0.243	11.443
P		0.157	<0.001	0.865	<0.001	0.745	<0.001	0.778	<0.001	0.808	<0.001

*p<0.05 *vs*. before treatment within the group.

sIgE, Dp-sIgE, and Df-sIgE levels

The sIgE, Dp-sIgE, and Df-sIgE levels did not exhibit statistically significant differences between the experimental and control groups before treatment ($p>0.05$), and they were lower in the experimental group than in the control group after treatment ($p<0.05$) (Table 5).

Predictive values of sIgE, Dp-sIgE, and Df-sIgE levels

The effective group had lower sIgE, Dp-sIgE, and Df-sIgE levels than the ineffective group ($p<0.05$) (Table 6). The plotted ROC curves revealed that the areas under the ROC curves (AUC) of sIgE, Dp-sIgE, Df-sIgE, and their combination for predicting the efficacy of mite-specific SCIT in treating AR was 0.839 [95%

confidence interval (CI): 0.757-0.921], 0.779 (95% CI: 0.684-0.874), 0.814 (95% CI: 0.719- 0.910), and 0.903 (95% CI: 0.842-0.963), respectively (Table 7 and Figure 1).

Table 5. sIgE, Dp-sIgE, and Df-sIgE levels before and after treatment [($\bar{x}$ ± s), lg IU/mL].

Group	n	sIgE		Dp-sIgE		Df-sIgE	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	49	2.53±0.45	1.76±0.39*	1.53±0.59	1.37±0.24*	1.28±0.64	1.02±0.26*
Experimental	49	2.57±0.38	1.32±0.38*	1.52±0.57	1.12±0.26*	1.27±0.61	0.84±0.31*
t		0.475	5.656	0.085	4.946	0.079	3.114
P		0.636	<0.001	0.932	<0.001	0.937	0.002

*p<0.05 *vs*. before treatment within the group.

Table 6. sIgE, Dp-sIgE, and Df-sIgE levels after the treatment in the effective and ineffective groups [($\bar{x}$ ± s), lg IU/mL].

Group	n	sIgE	Dp-sIgE	Df-sIgE
Effective	44	1.27±0.30	1.08±0.13	0.78±0.26
Ineffective	54	2.82±0.29	1.76±0.21	1.45±0.14
t		8.574	10.972	10.779
P		<0.001	<0.001	<0.001

Table 7. Predictive values of sIgE, Dp-sIgE, and Df-sIgE levels for the efficacy of mite-specific SCIT in treating AR.

Factor	AUC	Cut-off value	95% CI	P	Specificity	Sensitivity	Jorden index
sIgE	0.839	1.705lg IU/mL	0.757-0.921	<0.001	0.841	0.667	0.508
Dp-sIgE	0.779	1.215lg IU/mL	0.684-0.874	<0.001	0.750	0.656	0.406
Df-sIgE	0.814	0.965lg IU/mL	0.719-0.910	<0.001	0.795	0.642	0.437
Combination	0.903	-	0.842-0.963	<0.001	0.909	0.682	0.591

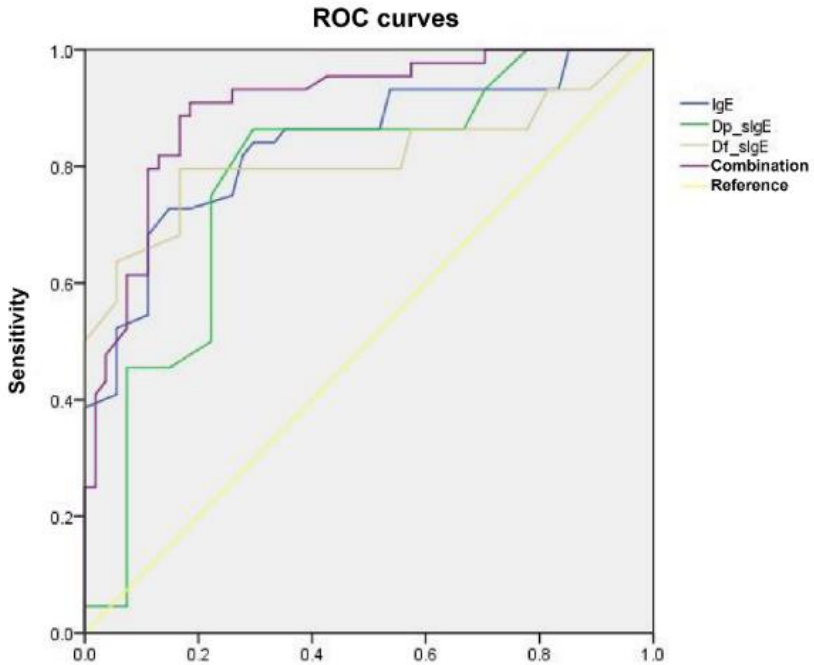

Figure 1. ROC curves for predictive values of sIgE, Dp-sIgE, and Df-sIgE levels for the efficacy of mite-specific SCIT in treating AR.

4. Discussion

AR is an IgE-mediated hypersensitive disease of the nasal mucosa after exposing the organism to allergens. Its incidence rate has increased as the living environment continuously changes. An

epidemiological statistical survey stated that the incidence of standardized AR in adults in China rose from 11.1% in 2005 to 17.6% in 2011 and is still growing (Chinese Journal of Otolaryngology Head and Neck Surgery Editorial Board, 2022).

AR is mainly treated with drug therapy and immunotherapy in clinical practice. Conventional Western medicine therapies have a rapid effect with satisfactory outcomes in some patients, but their long-term application still causes several adverse effects. Therefore, these treatments are not the first choice in clinical practice (Besh et al. 2020). Immunotherapy is a clinically recognized effective approach for AR. Immunomodulatory interventions during the natural course of AR prevent it from progressing into allergic asthma and relieve clinically relevant symptoms after continuous treatment. Immunotherapy improves the clinical outcomes of patients and reduces treatment expenses and economic burdens (Gellrich et al. 2020; Durham et al. 2023).

Valero et al. (2022) analyzed the efficacy of dust mite-specific SCIT to treat moderate-severe AR, finding that symptom scores significantly decreased after two months of SCIT, and the quality of life significantly improved after 12 months of treatment. Huang et al. (2022) conducted a retrospective analysis by performing SCIT with Mp allergen preparation in 372 patients with Mp-induced AR for three years or longer. They found that standardized SCIT might be a safe and effective treatment method for AR patients. The experimental group in this study had a higher total response rate (59.18% *vs*. 30.61%) and lower post-treatment TCS, VAS score, and miniRQLQ score than the control group. That means that mite-specific SCIT is markedly effective in treating AR patients, relieving clinical symptoms, and improving quality of life, similar to the findings in the mentioned studies. That may be attributed to the following factors: (i) Mite-specific SCIT regulates the thresholds of mast cells and basophils to reduce the IgE-mediated release of related histamine (Gioacchino et al. 2022); (ii) Mite-specific SCIT reduces the synthesis of activated eosinophils at the inflammatory site to repress the release of cationic proteins and relevant chemokines from eosinophils and neutrophils to some extent, thereby improving clinical symptoms; (iii) Mite-specific SCIT induces the production of Treg cells and the release of numerous immunosuppressive cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), by hindering the maturation of dendritic cells (DCs), which convert antibodies produced by B cells into IgG4, thus hindering the pro-antigen-presentation of IgE, reducing inflammatory factor expression, and enhancing efficacy (Liu et al. 2020).

IgE is significant for AR development and progression (Hesse et al. 2018; Feng et al. 2019), but its specific regulatory mechanism has not been elucidated. Bai et al. (2023) reported that type-2 inflammation and IgE were vital for AR, existed independently or comorbidly, and were somewhat related to the severity of clinical symptoms. Xue et al. (2020) found that sIgE, Dp-sIgE, and Df-sIgE antibody levels might predict the therapeutic effect, and the higher the expression of these indicators, the more likely the satisfactory therapeutic outcome for patients (20). These findings suggest that IgE is highly significant for AR. This study demonstrated that sIgE, Dp-sIgE, and Df-sIgE levels were lower in the experimental group than in the control group after treatment, proposing that mite-specific SCIT improves IgE levels. Such levels were lower in the effective group than in the ineffective group after treatment. The plotted ROC curves revealed that the AUC of sIgE, Dp-sIgE, Df-sIgE, and their combination for predicting the efficacy of mite-specific SCIT in AR treatment was 0.839 (95% CI: 0.757-0.921), 0.779 (95% CI: 0.684-0.874), 0.814 (95% CI: 0.719-0.910), and 0.903 (95% CI: 0.842-0.963), respectively. That indicates that monitoring sIgE, Dp-sIgE, and Df-sIgE levels may predict efficacy, corroborating the described findings.

5. Conclusions

Mite-specific SCIT is markedly effective in treating AR patients, relieving clinical symptoms, and improving quality of life. Its action mechanism may relate to the improvement of IgE expression levels.

Authors' Contributions: SUN, G.: Study concept and study design; HE, S.: study design and data collection and analysis; ZHANG, Q.: data collection and analysis and whiting.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

Ethics Approval: Not applicable.

Funding: This study was not financially supported.

References

ALVARO-LOZANO, M., et al. EAACI Allergen Immunotherapy User's Guide. *Pediatric Allergy and Immunology.* 2020, **31 Suppl 25**, 1-101. https://doi.org/10.1111/pai.13189

AUN, M.V., et al. Diphteria-tetanus-pertussis vaccine reduces specific IgE, inflammation and remodelling in an animal model of mite-induced respiratory allergy. *Vaccine*. 2020, **38**(1), 70-8. https://doi.org/10.1016/j.vaccine.2019.09.095

BAI, J. and TAN, B.K. B Lineage Cells and IgE in Allergic Rhinitis and CRSwNP and the Role of Omalizumab Treatment. American *Journal of Rhinology* Allergy. 2023, **37**(2): 182-92. https://doi.org/10.1177/19458924221147770

BESH, L., SLYUZAR, Z. and MATSYURA, O. Optimization Of Allergen-Specific Immunotherapy In Children With Bronchial Asthma: Selection Features, Patient Monitoring And Efficacy. *Georgian Med News.* 2020, **306**(306), 67-72. PMID: 33130649.

BOONPIYATHAD, T., et al. Der p 1-specific regulatory T-cell response during house dust mite allergen immunotherapy. *Allergy.* 2019, **74**(5), 976-85. https://doi.org/10.1111/all.13684

BOUSQUET, J., et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *Journal of Allergy and Clinical Immunology.* 2020, **145**(1), 70-80.e3. https://doi.org/10.1016/j.jaci.2019.06.049

CHENG, L., et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. *Allergy, Asthma & Immunology Research.* 2018, **10**(4), 300-53. https://doi.org/10.4168/aair.2018.10.4.300

CHINESE JOURNAL OF OTOLARYNGOLOGY HEAD AND NECK SURGERY EDITORIAL BOARD, RHINOLOGY GROUP, CHINESE MEDICAL ASSOCIATION OTOLARYNGOLOGY HEAD AND NECK SURGERY SOCIETY. Chinese Guidelines for diagnosis and treatment of allergic rhinitis (2022, Revised edition). *Chinese Journal of Otolaryngology Head and Neck Surgery.* 2022, **57**(2), 392-404. https://doi.org/10.3760/cma.j.cn115330-20211228-00828

DURHAM, S.R. and SHAMJI, M.H. Allergen immunotherapy: past, present and future. *Nature Reviews Immunology.* 2023, **23**(3), 317-28. https://doi.org/10.1038/s41577-022-00786-1

FENG, M., ZENG, X. and LI, J. House dust mite subcutaneous immunotherapy in Chinese patients with allergic asthma and rhinitis. *Journal of Thoracic Disease.* 2019, **11**(8), 3616-25. https://doi.org/10.21037/jtd.2019.06.35

GELLRICH, D., et al. De novo sensitization during subcutaneous allergen specific immunotherapy - an analysis of 51 cases of SCIT and 33 symptomatically treated controls. *Science Reports.* 2020, **10**(1), 6048. https://doi.org/10.1038/s41598-020-63087-4

GIOACCHINO, M., et al. Real-Life Effectiveness of Subcutaneous Immune Therapy with Carbamylated Monomeric Allergoids on Mite, Grass, and Pellitory Respiratory Allergy: A Retrospective Study. *Japanese Clinical Medicine.* 2022, **11**(24), 7384. https://doi.org/10.3390/jcm11247384

HAMED, A., et al. Nasal IgE production in allergic rhinitis: Impact of rhinovirus infection. *Clinical & Experimental Allergy.* 2019, **49**(6), 847-52. https://doi.org/10.1111/cea.13372

HESSE, L., et al. Subcutaneous immunotherapy with purified Der p1 and 2 suppresses type 2 immunity in a murine asthma model. *Allergy.* 2018, **73**(4), 862-74. https://doi.org/10.1111/all.13382

HUANG, H.H., et al. Efficacy comparison and safety analysis of subcutaneous specific immunotherapy with standardized house dust mite allergen in patients with single and multiple allergic rhinitis. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2022, **56**(6), 774-83. https://doi.org/10.3760/cma.j.cn112150-20220120-00071

LIU, Z., et al. Predictive methods for efficacy of house dust mite subcutaneous immunotherapy in allergic rhinitis patients: a prospective study in a Chinese population. *Internet Forum Allergy Rhinology.* 2020, **10**(3), 314-9. https://doi.org/10.1002/alr.22508

SHAMJI, M.H., et al. Diverse immune mechanisms of allergen immunotherapy for allergic rhinitis with and without asthma. *Journal of Allergy and Clinical Immunology.* 2022, **149**(3), 791-801. https://doi.org/10.1016/j.jaci.2022.01.016

VALERO, A., et al. Efficacy of subcutaneous house dust mite immunotherapy in patients with moderate to severe allergic rhinitis. *Immunotherapy.* 2022, **14**(9), 683-94. https://doi.org/10.2217/imt-2021-0353

WANG, C., et al. Chinese Guideline on Allergen Immunotherapy for Allergic Rhinitis: The 2022 Update. *Allergy, Asthma & Immunology Research.* 2022, **14**(6), 604-52. https://doi.org/10.4168/aair.2022.14.6.604

XUE, J.R., et al. Observation and analysis of systemic reactions to house dust mite subcutaneous immunotherapy in 362 patients with allergic rhinitis. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2020, **55**(5), 445-51. https://doi.org/10.3760/cma.j.cn115330-20200426-00333

Received: 18 September 2023 | **Accepted:** 27 July 2024 | **Published:** 16 October 2024