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ORIGINAL RESEARCH

Reduction in Artemisia Pollen-Specific IgE Levels During House Dust Mite Allergen Immunotherapy in Polysensitized Allergic Rhinitis Patients: A Three-Year Retrospective Study in Northern, China

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Background: Allergen immunotherapy (AIT) is a well-established treatment for allergic diseases, particularly in patients with allergic rhinitis and asthma. In regions where patients are polysensitized, AIT can have broader immunomodulatory effects. This study investigates the impact of house dust mite AIT on IgE responses to both dust mites and non-target allergens, specifically Artemisia pollen, in polysensitized allergic rhinitis patients.

Methods: This retrospective study included polysensitized patients aged 18 or older with a diagnosis of allergic rhinitis or rhinitis with asthma and positive IgE for both house dust mites and Artemisia pollen. Patients who completed at least three years of AIT for house dust mites were included. IgE levels for *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), and Artemisia pollen were measured at baseline and after 1, 2, and 3 years of treatment. Clinical outcomes were also recorded, including Total Nasal Symptom Score (TNSS), Visual Analog Scale (VAS), and medication use.

Results: Over three years, SIgE levels for Der p significantly decreased ($p = 0.0001$), while Der f showed a slight and significant decrease ($p = 0.0334$). Artemisia pollen-specific IgE decreased modestly ($p = 0.0478$), despite not being the target allergen. Total IgE levels increased slightly without statistical significance ($p = 0.9026$). Clinical outcomes improved significantly, with reductions in TNSS, VAS, and medication scores (all $p < 0.0001$), alongside a decrease in eosinophil counts, reflecting clinical and immunological benefits.

Conclusion: House dust mite AIT not only reduces dust mite-specific IgE levels but also leads to unexpected reductions in IgE levels for non-target allergens, such as Artemisia pollen. This suggests that AIT has broader immunological benefits, improving overall tolerance to multiple allergens in polysensitized patients.

Keywords: allergic rhinitis, allergen immunotherapy, dust mite, pollen, IgE, specific IgE, retrospective, polysensitized, treatment

Introduction

Allergic rhinitis (AR) is a chronic, recurrent inflammatory nasal disease mediated by IgE, which is non-infectious.[1] Its incidence has been increasing year by year. In addition to the common symptoms such as sneezing, runny nose, itching, and nasal congestion, AR may also affect sleep, daily activities, and quality of life. The high prevalence of AR, its complex and unresolved pathogenesis, and the ongoing unmet therapeutic needs have resulted in a significant burden on

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the societal economy.[2,3] Although the treatment of allergic rhinitis (AR) has made some progress in recent years with the continued in-depth study of its pathogenesis, there remain unmet therapeutic needs. Some biological agents currently available, including dupilumab targeting IL-4/13, omalizumab targeting IgE, and mepolizumab, reslizumab, and benralizumab targeting IL-5, have shown good efficacy and safety in clinical practice.[4,5] However, even with biologics that demonstrate superior efficacy, challenges remain regarding the long-term safety, and how to reduce dosage and manage relapse after discontinuation of treatment.[6] Allergen immunotherapy (AIT) is an effective, long-term treatment for IgE-mediated allergic diseases, particularly for patients with allergic rhinitis and asthma. AIT is the only effective causal treatment for allergic rhinitis. It can induce long-term clinical tolerance to the sensitizing allergens. Typically, clinical tolerance is induced after at least 3 years of AIT administration.[7,8] AIT modulates the immune system's response to allergens, reducing the severity of symptoms and, in some cases, preventing the development of new sensitizations.[9,10]

In northern China, key allergens such as house dust mites and Artemisia pollen are highly prevalent, contributing to a significant burden of allergic diseases, including allergic rhinitis and asthma. These allergens are common triggers for polysensitization, where individuals develop allergic reactions to multiple sources, such as both indoor and outdoor allergens. House dust mites, particularly *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f), are major indoor allergens, while Artemisia pollen is a dominant outdoor allergen, especially prevalent during late summer and autumn. Due to this widespread exposure, many patients in this region are sensitized to both dust mites and pollen, which complicates the management of allergic conditions.[11–14] Successful allergen immunotherapy (AIT) can induce the restoration of tolerance to allergens, making it a disease-modifying treatment. Establishing long-term clinical tolerance to allergens involves a complex network of interactions that regulate the functions of basophils, mast cells, allergen-specific regulatory T cells, B cells, and the production of specific antibodies. The reduction in symptoms and clinical improvement is achieved by shifting the immune response away from allergic inflammation and toward the development of immune tolerance.[15,16] While AIT is typically aimed at treating one specific allergen, AIT may have broader effects on the immune system, potentially influencing IgE responses to non-target allergens as well. Investigating how AIT impacts IgE levels for these non-target allergens can offer valuable insights into immune cross-reactivity and the mechanisms behind the development of immune tolerance, potentially providing broader benefits for polysensitized patients beyond the primary target allergen. Therefore, the purpose of this retrospective study is to investigate the changes in specific IgE levels for other allergens in polysensitized patients receiving house dust mite AIT, with a particular focus on Artemisia pollen.

Materials and Methods

Study Design and Patient Selection

This study complies with the Declaration of Helsinki. This retrospective study was designed to investigate the broader impacts of allergen immunotherapy (AIT) on IgE responses in polysensitized patients, specifically focusing on changes in IgE levels for both the targeted (house dust mites) and non-targeted allergens (Artemisia pollen). The study aimed to explore the potential implications of these changes for the management of polysensitized allergic rhinitis patients over three years. We included polysensitized patients aged 18 years or older who had been diagnosed with allergic rhinitis or allergic rhinitis with asthma and tested positive for specific IgE to both house dust mites and Artemisia pollen. All patients were required to have completed at least three years of house dust mite allergen immunotherapy (AIT) with Alutard SQ® (ALK), a standard form of AIT for dust mites. Additionally, the study included only those patients who had available data on total IgE and specific IgE levels at baseline, and follow-up visits at 1-year, 2-year, and 3-year intervals (Figure 1).

Exclusion Criteria

Several criteria were applied to ensure the homogeneity and integrity of the study sample. Patients were excluded from the analysis if they were receiving biological treatments during the follow-up period, as these treatments could influence IgE levels and confound the results. Other exclusion criteria included patients with incomplete data, those who dropped out of the study, or those with underlying medical conditions that could affect IgE levels, such as immunodeficiency, autoimmune disorders, or chronic infections. Pregnant or breastfeeding patients were also excluded to prevent any potential confounding effects of these conditions on the immune system and treatment outcomes.

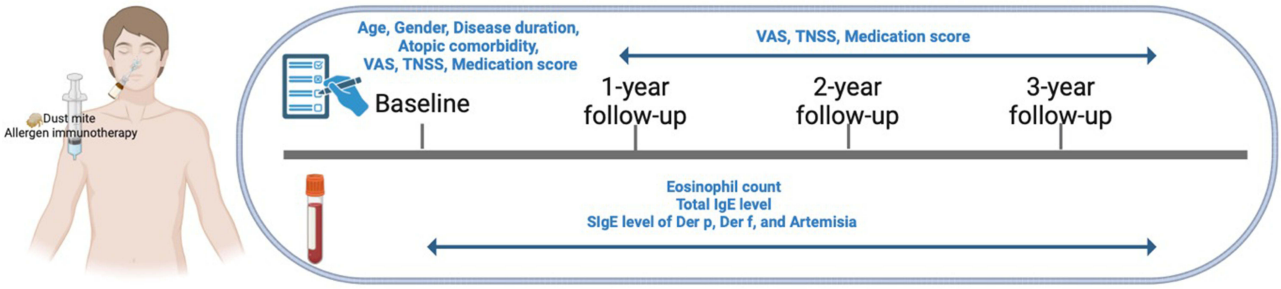

Figure 1 Study Design and Timeline. The study followed a cohort of polysensitized allergic rhinitis patients who underwent house dust mite allergen immunotherapy (AIT). Data were collected at four key time points: baseline (prior to the start of AIT), and at 1-year, 2-year, and 3-year follow-up visits. At each visit, clinical outcomes including Visual Analog Scale (VAS), Total Nasal Symptom Score (TNSS), and medication score were recorded. Laboratory assessments included eosinophil count, total IgE levels, and specific IgE (SIgE) levels for *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), and Artemisia pollen.

Data Collection

Data for this study were collected from electronic medical records (EMRs) at four key time points: baseline (before starting AIT), 1-year, 2-year, and 3-year follow-up visits. At the baseline, demographic data including age, gender, and disease duration were recorded. Additionally, clinical data related to the severity of allergic rhinitis, including the presence of atopic comorbidities such as asthma or atopic dermatitis, were documented. To assess clinical outcomes, the Total Nasal Symptom Score (TNSS), a commonly used measure of rhinitis symptoms, was recorded. The Visual Analog Scale (VAS) was also used to evaluate the severity of symptoms over the past week, providing a more subjective measure of symptom burden. Medication use was noted to track any pharmacological interventions used by the patients over the study period.[17]

Laboratory Assessments

Laboratory data were collected at baseline and during each follow-up visit. The primary laboratory measures included total IgE levels, which were analyzed to assess overall allergic sensitization, and specific IgE (SIgE) levels for *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), and Artemisia pollen to monitor changes in sensitization to the target and non-target allergens over time. The eosinophil count was also measured as a marker of allergic inflammation, as elevated eosinophil levels are often associated with allergic conditions.

Follow-up and Clinical Re-Evaluations

During follow-up visits, clinical outcomes were re-evaluated, including TNSS, VAS, and medication scores. Laboratory tests were also repeated at each visit to track changes in total IgE, SIgE levels, and eosinophil count. These data were used to assess the effectiveness of the treatment and to determine how the immune system's response to both targeted and non-targeted allergens evolved over the course of AIT. By following these patients over three years, the study aimed to explore the broader immunological effects of AIT, including the potential for cross-reactivity between allergens and its implications for long-term immune tolerance development. This longitudinal data allowed for a detailed examination of how IgE levels for both house dust mites and Artemisia pollen changed over time, and how these changes corresponded to improvements in clinical symptoms and overall disease management.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism (version 8.0). Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution assessed by the Shapiro–Wilk test. Categorical variables were summarized using counts and percentages. To evaluate longitudinal changes over time (baseline, 1-year, 2-year, and 3-year), repeated measures were analyzed using repeated measures ANOVA for normally distributed variables or Friedman test for non-parametric data. Post hoc comparisons between baseline and year 3 were performed using paired t-tests or Wilcoxon signed-rank tests, depending on normality. The clinical outcome measures (TNSS, VAS, and medication scores) and laboratory parameters (total IgE, SIgE for Der p, Der f, and Artemisia pollen, eosinophil

counts) were compared at multiple time points, and key changes from baseline to the third year were also highlighted. Associations between changes in IgE levels and clinical outcomes were assessed using Spearman's rank correlation. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

Patient Demographics and Baseline Characteristics

A total of 160 polysensitized patients completed the three-year follow-up and were included in the analysis (Table 1). The mean age of the patients was 31.78 ± 10.53 years, with a gender distribution of 103 males (64%) and 57 females (36%). The mean disease duration was 61.28 ± 29.61 months. In terms of atopic comorbidities, 16.25% of patients had asthma, 10.625% had atopic dermatitis, and 20.625% had allergic conjunctivitis, reflecting the polysensitized nature of the cohort. At baseline, the median total IgE level was 205.5 kU/L (IQR: 112.0–525.8). The specific IgE levels for *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), and Artemisia pollen were 10.85 kU/L (IQR: 0.94–56.80), 9.38 kU/L (IQR: 0.96–35.70), and 0.97 kU/L (IQR: 0.52–2.34), respectively. These values reflect a cohort with significant allergic sensitization to both dust mites and pollen.

Changes in IgE Levels Over Time

Over the course of the three-year follow-up, significant reductions were observed in specific IgE (SIgE) levels for the targeted allergens, Der p and Der f, as well as for the non-target allergen, Artemisia pollen (Figure 2 and Table 2). Total IgE levels increased slightly from 205.5 to 215.5 kU/L, but this change was not statistically significant (p = 0.9026). SIgE levels for Der p decreased from a baseline of 10.85 kU/L (IQR: 0.94–56.80) to 8.84 kU/L (IQR: 2.425–46.35) by year 3 (p = 0.0001), reflecting a significant reduction in IgE sensitization to dust mites. SIgE levels for Der f showed a similar trend, SIgE levels for Der f decreased slightly from 9.495 to 9.38 kU/L (p = 0.0334). Artemisia pollen-specific IgE demonstrated a more notable reduction, from 0.97 kU/L (IQR: 0.52–2.34) at baseline to 0.905 kU/L (IQR: 0.5225–1.56) by year 3 (p = 0.0478). This decrease in Artemisia-specific IgE levels suggests that AIT targeting house dust mites may also impact IgE responses to non-target allergens.

Clinical Outcomes

Marked clinical improvements were observed over the three years of AIT treatment. The Total Nasal Symptom Score (TNSS), which reflects the severity of nasal symptoms, significantly decreased from a baseline median of 5 (IQR: 4, 6)

Table 1 Demographic Data of Included Patients

Demographic Data	Baseline
Age (years, Mean ± SD)	31.78 ± 10.53
Gender (Male/Female)	103/57
Disease Duration (months, Mean ± SD)	61.28 ± 29.61
Atopic comorbidity (n, %)	Asthma (26, 16.25%) Atopic dermatitis (17, 10.625%) Food allergy (5, 3.125%) Medication allergy (3, 1.875%) Allergic conjunctivitis (33, 20.625%)

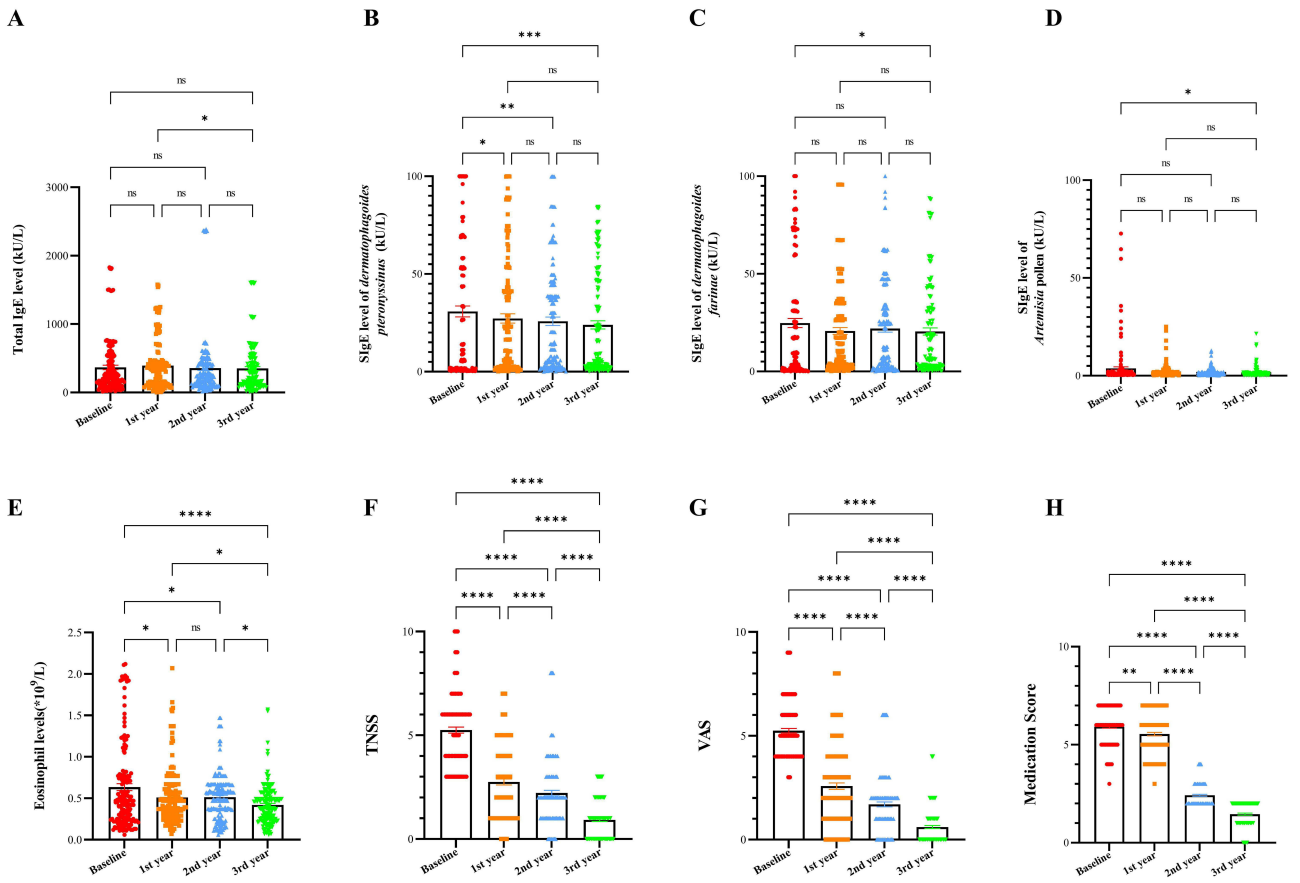

Figure 2 Immunological and Clinical Changes in Polysensitized Allergic Rhinitis Patients Undergoing House Dust Mite-AIT Over Three Years. (**A**) Total IgE Levels (kU/L): Total serum IgE levels measured at baseline, 1st year, 2nd year, and 3rd year of AIT. (**B**) Specific IgE (SIgE) to *Dermatophagoides pteronyssinus* (Der p) (kU/L): SIgE levels to Der p before and during AIT. (**C**) Specific IgE (SIgE) to *Dermatophagoides farinae* (Der f) (kU/L): SIgE levels to Der f at different time points. (**D**) Specific IgE (SIgE) to Artemisia Pollen (kU/L): SIgE levels to Artemisia pollen before and during AIT. (**E**) Eosinophil Count ($\times 10^9$/L): Peripheral eosinophil levels show changes over the treatment period. (**F**) Total Nasal Symptom Score (TNSS): Clinical symptom severity assessed using TNSS, decreasing significantly over time. (**G**) Visual Analog Scale (VAS) Score: Subjective symptom severity assessed via VAS, demonstrating marked improvement. (**H**) Medication Score: Reduction in medication use throughout AIT. Data are shown as scatter plots with median and interquartile ranges. Statistical significance is indicated as follows: *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.
Abbreviation: ns, not significant.

to 1 (IQR: 0, 2) by year 3 ($p < 0.0001$), indicating a substantial reduction in nasal symptoms. The Visual Analog Scale (VAS) score, which measures the overall severity of symptoms, also showed a significant decrease, from 5 (IQR: 4, 6) at baseline to 0 (IQR: 0, 1) ($p < 0.0001$), further confirming symptom improvement. Additionally, the medication score, which reflects the amount of pharmacological intervention required, decreased significantly from 6 (IQR: 5, 7) at baseline to 2 (IQR: 1, 2) by year 3 ($p < 0.0001$). This suggests that AIT reduced the need for medications such as antihistamines, corticosteroids, and bronchodilators, further supporting its efficacy.

Laboratory Measures

Laboratory assessments, including eosinophil count, were conducted at each time point. Eosinophil levels were elevated at baseline (0.47×10^9/L [IQR: 0.25, 0.77]) and decreased over time, with the lowest median value recorded at 0.38×10^9/L [IQR: 0.24, 0.56] by year 3 ($p < 0.0001$). This decline in eosinophil counts reflects reduced allergic inflammation following AIT.

Discussion

In this study, we observed that house dust mite allergen immunotherapy (AIT) not only reduces IgE levels specific to dust mites but also appears to have a broader impact, including a significant reduction in IgE levels for non-target allergens, specifically Artemisia pollen. This finding is particularly interesting as it suggests that AIT may influence the immune system

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Table 2 Clinical, and Laboratory Data Over 3 years of Included Patients

Clinical, and Laboratory Data	Baseline	1-Year	2-Year	3-Year	*P* value (Baseline vs 3-Year)
TNSS (Median [IQR])	5 (4, 6)	2 (1, 4)	2 (1, 3)	1 (0, 2)	<0.0001
VAS (Median [IQR])	5 (4, 6)	2 (1, 4)	2 (1, 2)	0 (0, 1)	<0.0001
Medication score (Median [IQR])	6 (5, 7)	6 (5, 6.75)	2 (2, 3)	2 (1, 2)	<0.0001
Total IgE (kU/L) (Median [IQR])	205.5 (112.0, 525.8)	339.5 (119.3, 446.0)	237.5 (117.0, 434.8)	215.5 (111.8, 492.3)	0.9026
Eosinophil levels (*10^9/L) (Median [IQR])	0.4700 (0.2500, 0.7700)	0.4200 (0.2900, 0.6400)	0.5500 (0.3375, 0.6600)	0.3800 (0.2425, 0.5600)	<0.0001
SIgE level of *Dermatophagoides pteronyssinus* (Der p, kU/L) Median [IQR]	10.85 (0.9400, 56.80)	16.40 (2.353, 42.73)	14.00 (2.435, 38.70)	8.840 (2.425, 46.35)	0.0001
SIgE level of *Dermatophagoides farinae* (Der f, kU/L) Median [IQR]	9.495 (2.463, 32.18)	13.90 (3.400, 34.80)	12.35 (2.300, 33.88)	9.380 (0.9600, 35.70)	0.0334
SIgE level of Artemisia pollen (kU/L) Median [IQR]	0.9700 (0.5200, 2.343)	1.310 (0.8050, 2.285)	1.220 (0.6825, 2.280)	0.9050 (0.5225, 1.560)	0.0478

Notes: Normally distributed variables, including age, disease duration, TNSS, VAS, and medication score, are presented as Mean ± SD. Median [IQR] is used for skewed data, including total IgE, eosinophil levels, and SIgE values. TNSS (Total Nasal Symptom Score) is measured on a scale of 0 to 12, with higher scores indicating more severe nasal symptoms. VAS (Visual Analog Scale) measures symptom severity, with patients rating their symptoms from 0 (no symptoms) to 10 (worst symptoms). The medication score is a composite of medication used for allergic symptoms, including antihistamines, corticosteroids, and bronchodilators. Total IgE and SIgE data were measured using the ImmunoCAP system (Phadia 250 and 1000, ThermoFisher Scientific, USA) according to the manufacturer's instructions and reported in kilo units per liter (kU/L).

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in a way that extends beyond the allergen it is intended to target. Clinically, our results show that AIT led to significant improvements in Total Nasal Symptom Scores (TNSS), Visual Analog Scale (VAS) scores, and medication use, which is consistent with other studies showing the benefits of AIT for allergic rhinitis and asthma. The improvement in eosinophil counts further supports the idea that AIT reduces allergic inflammation, contributing to the relief of symptoms. The reductions in *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) specific IgE levels were expected, as previous studies have shown that AIT is effective in targeting the specific allergens it is designed for. Our results are in line with these findings, with a significant decrease in IgE levels for dust mites over the three years. However, the decrease in Artemisia pollen-specific IgE was more surprising, as this was not the target allergen of AIT in this study. The reduction in Artemisia-specific IgE suggests that AIT may have a broader effect on the immune system, potentially affecting the response to other allergens that share similar protein structures with the target allergen.

The interesting phenomenon that allergen-specific immunotherapy (AIT) targeting house dust mites can also reduce Artemisia pollen-specific IgE levels is not yet fully understood due to the complexity of AIT's immune mechanisms. However, there are several potential mechanisms to explain this intriguing phenomenon within the context of AIT's immune mechanisms. One possible mechanism for this broader immune effect is immune cross-reactivity. Just as house dust mite-specific AIT can improve clinical and immunological outcomes in patients with multiple dust mite sensitivities beyond the single sensitization to dust mites, previous studies have confirmed that AIT targeting a single dust mite species for patients with multiple dust mite sensitizations shows no significant difference in clinical outcomes compared to AIT targeting multiple dust mite species. This effect is due to immune cross-reactivity between dust mites. However, there is currently no research confirming the immune cross-reactivity between house dust mites and Artemisia pollen, nor has it been explored further whether there are structural similarities in these allergens that may lead to the immune system recognizing them in a similar way. This could result in broader immune effects or outcomes. This suggests that by desensitizing the immune system to dust mites through AIT, the immune response to related allergens, such as Artemisia pollen, could also be reduced, emphasizing the necessity for further research into the immune cross-reactivity between house dust mites and Artemisia pollen.

Another potential mechanism is that AIT has been shown to promote the production of regulatory T cells (Tregs) and IgG4 antibodies.[7,9,10,16] Dynamic changes in IgG4 levels have been observed during AIT treatment, with specific IgG4 levels increasing exponentially from one week to one month, to six months, one year, and up to three years. By the later stages of AIT treatment, specific IgG4 levels were more than 100 times higher than baseline. This increase in IgG4 can reduce allergy-related symptoms, new sensitizations, and medication use, thereby reducing the burden and improving the quality of life.[18–20] Tregs help suppress excessive immune responses, while IgG4 antibodies act as blockers, preventing IgE from binding to allergens and triggering allergic reactions. This mechanism likely contributes to the observed reduction in IgE levels, not only for the primary allergen but also for non-target allergens that share similar epitopes. Additionally, in many allergic patients, a gradual expansion of the IgE response to sensitizing molecules is observed: from initial single-molecule to oligomolecular and eventually multi-molecular sensitization patterns. It can be inferred that the immune response is more easily modifiable in the early single-molecule phase than in the later multi-molecular phase, suggesting that the immune system is more readily adaptable and tolerant in the early stages of sensitization.[21,22]

However, there are limitations to this study. Its retrospective nature means that it relies on existing data, which may introduce bias or result in missing data. The absence of a control group also limits our ability to firmly establish a causal relationship between AIT and the observed changes in IgE levels. Moreover, this study was conducted in a specific population of northern China, so its findings may not be fully applicable to other regions with different allergen profiles or patient demographics. Future prospective studies with larger, more diverse populations and a control group are needed to validate these findings and further explore the mechanisms behind the broader effects of AIT. In conclusion, our study shows that house dust mite AIT not only reduces IgE levels specific to dust mites but also leads to a noticeable decrease in Artemisia pollen-specific IgE. This unexpected effect suggests that AIT may have a broader impact on the immune system, possibly influencing responses to allergens beyond the primary target. One explanation for this could be cross-reactivity, where allergens with similar protein structures trigger overlapping immune responses. AIT may help regulate the immune system by promoting the production of regulatory T cells and blocking antibodies like IgG4, which reduce IgE activity and allergic reactions.[9,23] This could explain why IgE levels for non-target allergens, such as Artemisia

pollen, also declined over time. Our findings suggest that AIT may offer added benefits for polysensitized patients by reducing their overall allergic burden and improving tolerance to multiple allergens.

Conclusion

In conclusion, our study suggests that house dust mite AIT offers more than just a targeted reduction in dust mite-specific IgE. We found that AIT also resulted in a significant decrease in IgE levels for non-target allergens like Artemisia pollen. This indicates that AIT may have broader effects on the immune system, potentially improving tolerance to multiple allergens in polysensitized patients. While the mechanisms behind these broader effects are still being explored, our findings highlight the potential of AIT to provide more comprehensive relief, reducing allergic symptoms and medication use. Despite the study's limitations, including its retrospective design and lack of a control group, the results offer promising insights into how AIT could be further utilized to treat complex allergic conditions. Further research is needed to confirm these findings and better understand the broader scope of AIT's benefits.

IRB Approval Status

This study was approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Shandong First Medical University, Shandong Provincial Qianfoshan Hospital.

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Disclosure

The authors declare that they have no relevant conflicts of interest in this work.

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