

Early Intervention Improves Clinical Responses to House Dust Mite Immunotherapy in Allergic Rhinitis Patients

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Keywords

Allergen-specific immunotherapy · Allergic rhinitis · House dust mite · Clinical response · Specific IgE

Abstract

Background: Allergen immunotherapy (AIT) is the unique causal treatment for respiratory allergy. As AIT is expensive and of long duration, the availability of a marker predicting AIT responders is of crucial relevance. **Objective:** To investigate clinical parameters correlated with effective AIT in allergic rhinitis (AR) patients. **Methods:** This is a prospective, nonrandomized open study in which a total of 284 AR patients who had received house dust mite (HDM) subcutaneous AIT were enrolled from January 2011 to December 2015, and then followed up for 3 consecutive years. Demographic data, clinical history, laboratory tests (specific and total IgE levels), symptoms score, concomitant medication, and adverse reactions during AIT were collected. An AIT responder patient was defined when a visual analog score (assessing global symptoms) had decreased by >30% compared to baseline and concomitant medication was equal to or less than before AIT. **Results:** Thirty-three patients dropped out, so 251 patients were analyzed; 175 (69.7%) patients were responders. This group had a higher baseline symptom score

than the AIT nonresponder group (7.5 vs. 6.9). A significant negative correlation was found between AR symptom duration and the clinical response to AIT. Local reactions (LRs) during AIT had a positive correlation. Other variables such as a family history of atopy, combined asthma history, and the levels of specific and total IgE had no correlations with effective AIT. **Conclusion:** Early intervention with AIT helps to improve the efficacy of AR treatment. LR might predict successful AIT. Highly symptomatic AR patients may develop increased clinical responses to AIT.

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Introduction

Allergic rhinitis (AR) affects up to 40% of the population worldwide, and some studies suggest that its incidence is increasing [1, 2]. Allergen immunotherapy (AIT) is the only potential disease-modifying treatment for allergic patients based on the long-term relief of symptoms even after treatment cessation. Numerous well-designed controlled studies have demonstrated that AIT is efficacious in the treatment of AR [3, 4]. However, conventional subcutaneous AIT administration schedules are time-consuming and expensive, AIT is not successful in

all AR patients, and real-life studies are needed [5]. Information taken from randomized controlled trials has dictated current guidelines, although AR patients recruited to these trials do not represent the wider spectrum of patients seen in clinical practice, because of the too-strict inclusion and exclusion criteria [5]. It is thus crucial for physicians to select appropriate patients to receive AIT. Available surrogate indicators to predict clinical responses are imperative and of great value in clinical practice. Although several studies have evaluated the role of relevant pretreatment factors including the levels of specific and total IgE (sIgE and tIgE), and also the sIgE/tIgE ratio, in predicting effective AIT, the results across studies are inconsistent [6–9]. Additionally, most studies are retrospectively designed and so the results have to be interpreted with caution. House dust mite (HDM) is the most common allergen in AR patients [10]. In this prospective study, we treated AR patients with standardized HDM AIT (Alutard SQ, ALK-Abelló, Hørsholm, Denmark) and followed them up for 3 years, with the intention being to search for and evaluate the factors with a potential for predicting who will be clinical responders to AIT.

Methods

Patients

A total of 284 AR patients who received HDM AIT were consecutively enrolled in our study from January 2011 to December 2015. The study was approved by the Independent Ethical Committee of Tongji Hospital and all the participants or their statutory guardians signed the informed consent. Consecutive patients enrolled in our study were those who: (1) were diagnosed with AR according to the ARIA guidelines [11], (2) showed positive skin prick tests to HDM and had serum HDM-sIgE levels ≥ 0.7 kU_A/L, and (3) had allergic symptoms of rhinitis after exposure to HDM. Resistance to previous pharmacotherapy was not an inclusion criterion. We excluded patients if they were allergic to other clinical relevant allergens (e.g. pollen and fungi, according to their history), had a serum sIgE level ≥ 0.7 kU_A/L, an autoimmune disease or a cardiovascular disorder, and who used β -blockers or ACE inhibitors. Patients with a history of asthma were carefully assessed in terms of asthma control, and had inhaled corticosteroids or inhaled corticosteroids/long-acting β_2 agonists prescribed, according to the GINA (Global Initiative for Asthma, available at www.ginasthma.org) guidelines. Other asthmatic medications such as antileukotrienes and systemic corticosteroids which might influence the symptoms of AR were forbidden during the study period.

Allergen Tests

Skin tests for 19 kinds of inhalant allergens were performed, including HDM, cockroach, mulberry silk, animal dander (cat, dog, sheep, and horse), tree pollen (*Sabina*, *Platanus*, *Populus*, and *Cryptomeria*), weed pollen (*Artemisia*, *Ambrosia*, and *Humulus*), and fungi (*Alternaria*, *Cladosporium*, *Aspergillus*, and *Paecilomyces*) (Macro-Union Pharmaceutical Co., Beijing China). Histamine (10 mg/mL) and diluent were used as positive and negative controls.

Serum sIgE and tIgE were measured by ImmunoCAP (Phadia, Thermo Fisher Scientific, Uppsala, Sweden) at baseline, and sIgE to HDM was reevaluated 1 year after AIT.

A positive skin reaction was defined as a wheal size of ≥ 3 mm, after subtraction of the negative control. The cutoff value of serum sIgE was 0.35 kU_A/L.

Allergen Immunotherapy

Standardized HDM allergen extracts with depot formulations (Alutard SQ) were used for AIT [12]. According to the manufacturer, the product was well-characterized (1 mL of 100,000 SQ-U containing 4.5 μ g Der p 1) [13]. There were 4 different vials (Nos. 1–4) of standardized allergen extracts, in which the allergen concentration increased 10-fold from 100 to 100,000 SQ-U/mL. The build-up phase was carried out with the conventional schedule provided by the manufacturer, with weekly injections of a volume of 0.2, 0.4, and 0.8 mL in vial Nos. 1–3, and 0.1, 0.2, 0.4, 0.8, and 1.0 mL in the No. 4 vial, reaching the maintenance dose of 100,000 SQ-U. The maintenance dose was then given on a 6-weekly basis according to the manufacturer's instructions. Pulmonary function testing was performed before and after each injection. The injection was delayed if the preinjection forced expiratory volume in 1 s (FEV₁) and/or peak expiratory flow were $<80\%$ of the predicted value. After each injection, patients were kept under observation for 30 min.

Assessment of Symptoms, Medication Use and Side Effects

The effectiveness of AIT was evaluated on the basis of a clinical response (a reduction in nasal symptoms) and any reduction in the pharmacotherapy that was being taken as needed (i.e. local or oral antihistamine medication, and if a nasal corticosteroid was prescribed, the duration was to be <1 week). A visual analog scale (VAS) of 0–10 was used to evaluate the severity of AR symptoms (including sneezing, itching, rhinorrhea, and nasal congestion): 0 for “no symptoms” and 10 for “very severe symptoms.” The rescue medications were assessed by recording drug consumption in the past 6 months at the baseline and at every visit. Rescue medication score was evaluated as 0–3, 0 for “taken no medication,” 1 for “taken less medication since AIT,” 2 for “taken equal medication since AIT,” and 3 for “taken more medication since AIT.” Patients globally evaluated both parameters every 6 months. A responder was defined on the basis of a VAS reduction of at least 30% after year 3, compared to the baseline VAS (before AIT) and a medication score of 0, 1, or 2. In all other cases, AIT was evaluated as ineffective. Both local and systemic side effects were analyzed according to international scores [14].

Statistical Methods

Descriptive parameters, such as means and standard deviations for normally distributed continuous data, median percentiles for nonnormally distributed continuous data and frequencies and percentages for categorical data, were calculated. The 2-sample *t* test or the nonparametric equivalent, the Mann-Whitney test, was used to evaluate the association between systemic reactions and continuous measures. The Pearson χ^2 test (Yates-corrected χ^2 if necessary) or the Fisher exact test was used to evaluate the association between systemic reactions and categorical measures. Odds ratios (ORs) be-

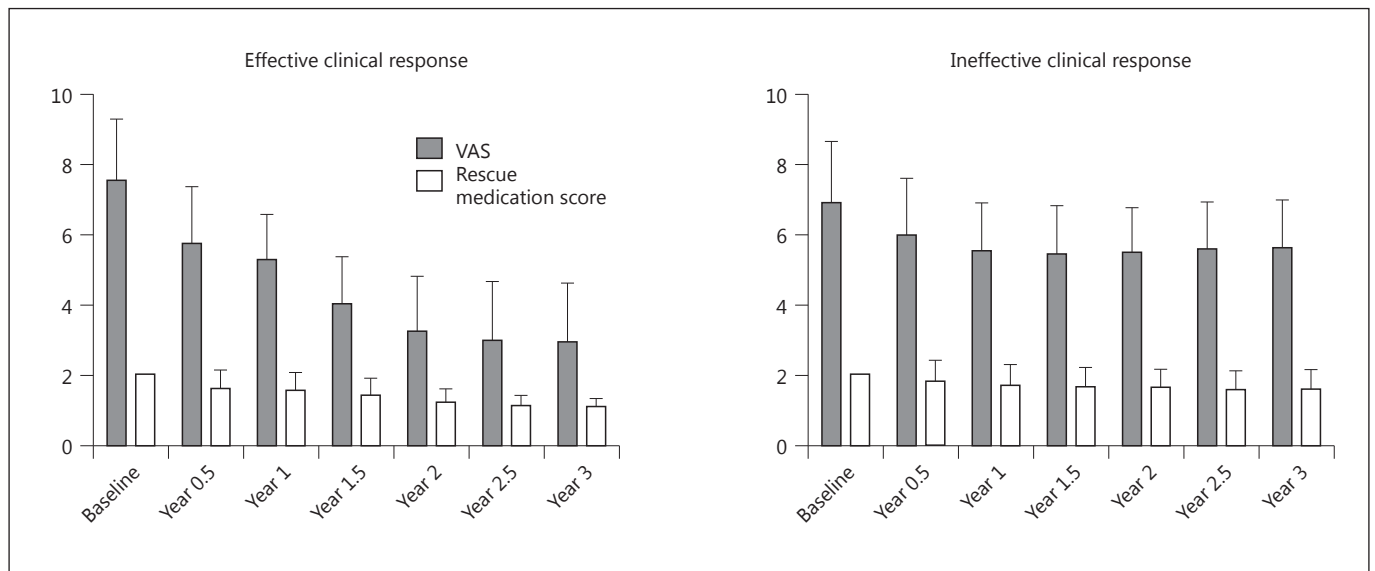


Fig. 1. VAS and rescue medication scores during AIT in the responder and nonresponder groups. In the responder group, VAS scores decreased consistently from baseline to year 2, and the scores at year 2 (3.2) and year 3 (2.9) were significantly lower than at baseline (7.5; $p < 0.0001$), but there was no difference in scores at the 2- and 3-year follow-ups ($p > 0.05$). The rescue medication

score at year 3 (1.1) was significantly lower than at baseline (2.0; $p < 0.0001$). In the nonresponder group, the VAS at year 0.5 (6.0) was lower than at baseline (6.9; $p < 0.05$); however, there was no difference in scores at the 0.5- and 3-year follow-ups (5.6; $p > 0.05$). The rescue medication score at year 3 (1.6) was lower than at baseline (2.0; $p < 0.0001$).

tween groups were calculated and 95% confidence intervals (CIs) generated. For the multivariable analysis, logistic regression, with forward model selection and the likelihood ratio test, was applied to assess the predictive model of the dependent variable. All tests were performed 2-tailed, and $p < 0.05$ was considered statistically significant. SigmaPlot software was used for all statistical analyses.

Results

Patient Characteristics

A total of 284 consecutive patients were recruited from the Allergy Department of Tongji Hospital, Wuhan, China, from January 2011 to December 2015. Thirty-three patients dropped out; reasons for this included a time-schedule conflict (17 patients), adverse reactions (6 patients), an improvement of symptoms (4 patients), economic difficulties (2 patients), poor efficacy (2 patients), and pregnancy (2 patients), meaning that 251 patients were analyzed. Of these, 160 (63.7%) were males. The mean age was 17.6 years (range 5–65 years) and the mean duration of AR was 5.3 years. The mean VAS score at baseline was 7.3; 83 (33.1%) had a history of asthma. Sixty-seven (26.7%) were multisensitized. None of them had already had AIT.

Clinical Responses to AIT

A response to AIT was recorded in 175 (69.7%) patients. The mean duration of symptoms (from time of first symptoms to initial AIT) in the responder group was 4.2 years, which was significantly shorter than that in the nonresponder group (7.8 years). The mean duration of symptoms was 5.3 years. The mean VAS score at baseline was higher in the responder group (7.5 ± 1.8) than in the nonresponder group (6.9 ± 1.8), but after 3 years of AIT, the VAS score was lower in the responder group (2.9 ± 1.7 vs. 5.6 ± 1.4 ; Fig. 1). After the initiation of AIT, patients were taking less medication over time (Fig. 1). Local reactions (LRs) occurred in 144/175 patients in the responder group, manifesting as an early wheal (113/144) and a late induration reaction (82/144), and in 36/76 in the nonresponder group (29/36 early wheals and 21/36 late induration reactions). Systemic reactions occurred in 25/175 patients in the responder group (grade 1 in 7/25, grade 2 in 15/25, and grade 3 in 3/25), and in 7/76 in the nonresponder group (grade 1 in 2/7, grade 2 in 4/7, and grade 3 in 1/7); no fatal reaction occurred in either group [14]. The incidence of LR during AIT was 82.3% in the responder group, significantly higher than in the nonresponder group (47.4%). There

Table 1. Characteristics of the patients with effective and ineffective clinical responses to AIT

Characteristic	Clinical response		<i>p</i> value
	effective	ineffective	
Patients	175 (69.7%)	76 (30.3%)	
Age, years ^a	17.5 (15.5–19.6)	17.7 (14.3–21.1)	0.913
BMI ^a	19.9 (19.3–20.5)	19.3 (18.4–20.2)	0.244
Males/females	117/58	43/33	0.158
Males	66.9%	56.6%	
Females	33.1%	43.4%	
Atopic family history (yes/no)	115/60	40/36	0.069
Positive history	65.7%	52.6%	
No history	34.3%	47.4%	
Multiple allergens (yes/no)	48/127	19/57	0.807
Multiallergens	27.4%	25.0%	
Monoallergen	72.6%	75.0%	
Food allergy (yes/no)	10/165	6/70	0.713
Positive	5.7%	7.9%	
Negative	94.3%	92.1%	
Infant eczema history (yes/no)	104/71	41/35	0.504
Positive history	59.4%	53.9%	
No history	40.6%	46.1%	
Rhinitis/asthma + rhinitis	115/60	53/23	0.634
Rhinitis	65.7%	69.7%	
Asthma + rhinitis	34.3%	30.3%	
Onset of symptoms, years ^a	4.2 (3.4–5.0)	7.8 (5.7–9.9)	0.026
Serum tIgE level, kU/L ^b	375.9 (325.3–435.3)	293.2 (239.8–358.6)	0.101
Serum sIgE level, kU/L ^b			
At baseline	40.1 (34.5–46.7)	37.7 (28.5–49.8)	0.795
At 1 year	42.2 (36.9–48.1)	39.3 (30.9–49.9)	0.883
Serum sIgE/tIgE ratio ^a	14.3 (12.7–15.9)	16.9 (14.3–19.6)	0.084
Local adverse reaction (yes/no)	144/31	36/40	<0.0001
Adverse reaction	82.3%	47.4%	
No reaction	17.7%	52.6%	
Systemic adverse reaction (yes/no)	25/150	7/69	0.367
Adverse reaction	14.3%	9.2%	
No reaction	85.7%	90.8%	

Values are expressed as *n*, unless otherwise indicated. Significantly different values are italicized.

^a Mean (range). ^b Geometric mean after logarithmic transformation (range).

were no differences between the 2 groups in gender distribution, atopy history, multi- or monosensitization, combined asthma history, serum sIgE level, and systemic reaction rate (Table 1).

A multiple logistic regression model was used to determine the independently predicting factor for the clinical response to AIT. Seven variables were included, but only 2 of these displayed statistical differences, i.e. the duration of AR symptoms (OR 0.920, 95% CI 0.877–0.965, *p* < 0.001) and local adverse reaction (OR 0.214, 95% CI 0.114–0.402, *p* < 0.001) (Table 2).

Discussion

AIT has been recommended by ARIA (Allergic Rhinitis and Its Impact on Asthma) as the only disease-modifying treatment for AR, and it is indicated for the treatment of moderate-to-severe symptoms of AR, especially in patients who do not respond well to pharmacotherapy [11]. However, AIT has been underused for a long time and is estimated to be used in <10% of patients with AR or asthma worldwide, despite its clinical efficacy and long-term benefits [15]. In most countries, AIT remains

Table 2. Multivariate analysis for independently predicting factors of a clinical response to AIT

Variable	OR	95% CI	<i>p</i> value
Gender	0.747	0.398–1.399	0.085
BMI	1.095	0.998–1.201	0.056
Atopic family history	0.785	0.421–1.464	0.447
Onset of symptoms	0.920	0.877–0.965	<0.001
Serum tIgE level	1.001	1.000–1.001	0.090
Serum sIgE/tIgE ratio	0.746	0.040–13.862	0.844
Local adverse reaction	0.214	0.114–0.402	<0.001

Significantly different values are italicized.

a secondary option to drugs that treat symptoms, due to the cost, the perceived long duration of treatment, safety, and individual efficacy. Correct selection of patients is crucial, and, as such, AIT should only be offered to patients who meet the indications, as stipulated in recent guideline documents. AIT responder rate may range between 60 and 90% of AIT prescription [16]. As AIT is expensive and of long duration, a marker able to predict successful AIT is urgently needed. This issue has been the topic of several investigations; however, the results obtained in one study often fail to be confirmed in another [7, 9], so, presently, a sure marker for predicting AIT response is still lacking.

We thus conducted an open, observational, prospective study to analyze responses to AIT, seeking to evaluate the potential markers for predicting AIT responders. We found that the AIT responder group had a shorter duration of AR symptoms than the AIT nonresponder group, which implies that early intervention for AR patients will help to improve the clinical responses to AIT. The EAACI (European Academy of Allergy and Clinical Immunology) stated in its position paper that AIT should be initiated early in the course of allergic disease, in order to prevent irreversible damage in the mucous membranes of the shock organ [17]. The WAO (World Allergy Organization) also suggest that the preventive benefits of AIT may be greater if initiated early in the course of the allergic disease, and that failure of pharmacological treatment is not an essential prerequisite for the use of AIT [18]. Several studies have reported that both airway remodeling and underlying allergic inflammation exist in patients with mild and moderate-to-severe AR [19, 20]. Our study provided new evidence in real life to support the early application of AIT in AR patients, not only for the relief of symptoms but also to possibly improve the clinical re-

sponse to the AIT itself. Thus, we suggest that AIT should be considered as the initial treatment once an AR diagnosis is confirmed and the relevant causal allergen has been identified.

LRs associated with AIT are fairly common, occurring in 26–82% of patients [21]. In our study, there was an LR rate of 76.1%, and higher in the AIT responder group (82.3%) than in the nonresponder group (47.4%). Our results also suggest that LR is associated with a greater risk of systemic reactions, which is consistent with our previous study [12]. However, we did not find a statistically significant difference in the rate of systemic reactions between the AIT responder group (14.3%) and the AIT nonresponder group (9.2%) (Table 1). In addition, our study indicated that a greater frequency of LR in AIT might be a predictor of future clinical responses to AIT, which was not shown in other studies. We speculate that the occurrence of LR indicates that the HDM vaccine is of an adequate bioactivity (and dose for a single patient) to trigger IgE-mediated reactions in the patient; this is essential for successful AIT; Moreno et al. [22] reported in their study that a dose response was observed for the clinical efficacy of HDM subcutaneous immunotherapy. We observed a sensitivity of LR to predict effective AIT of 82.3%, while the specificity was only 52.6%. However, this result should be interpreted with caution, and larger-sample studies are needed.

A certain level of symptoms is indeed necessary to demonstrate the activity of AIT. One post hoc analysis to evaluate the relationship between allergic disease severity and efficacy of pollen AIT showed that the more severe the disease, the greater the treatment effect [23]. In our study, highly symptomatic AR patients experienced an increased clinical efficacy of AIT. The AIT responder group had a higher baseline symptom score than the AIT nonresponder group (7.5 vs. 6.9); this score decreased consistently to a low level in the next 2 years, and was then maintained for 1 year. In the AIT nonresponder group, the symptom score changed only very slightly at the different visits during the 3-year follow-up. Our study showed that AIT had a more visible effect on the AR patients with more severe symptoms. However, this did not mean that patients with milder symptoms should be encouraged to wait until they demonstrate more severe symptoms before seeking AIT treatment. A previous study showed the duration of AR symptoms to correlate positively with AR severity domains in Chinese patients [24]. In our study, 172 patients had severe symptoms (a VAS score of ≥ 7), and 96 (55.8%) of these had an AR history of < 3 years. On the contrary, 41 patients had mild-

to-moderate symptoms (a VAS score of ≤ 5), 17 (41.5%) with an AR history of >3 years. This implies that a prolonged disease period does necessarily correspond with more symptoms. We found that the mean duration of AR was shorter in AIT responders, thus we suggest that AIT can be initiated early rather than wait until the disease worsens. Our study also indicated that the efficacy of AIT can be observed 6 months after AIT is initiated. We suggest that AIT should be discontinued when there has been no improvement in AR symptoms after 1 year.

We evaluated several other variables to predict AIT clinical responses, including age, gender, a history of family atopy, combined asthma history, allergen sensitization status, serum sIgE level, etc. However, we failed to establish the correlation between these variables and AIT responses. We testified to several predictive indicators presented in previous studies, such as sIgE level (cutoff 10 kU/L), sIgE/tIgE ratio (cutoff 16%) and tIgE level (cutoff 965 kU/L) [6, 7, 25], and here, interestingly, we found that there were no differences between the AIT responder and nonresponder groups. This discrepancy also exists in other studies [9], indicating the heterogeneity of different studies (e.g. race, region, age, molecular sensitization pattern to HDM component, etc.), and the need for reliable predictive factors to determine AIT responders is still currently unmet.

In conclusion, our study found that AIT responders had a shorter duration of AR symptoms, a greater fre-

quency of LRs during AIT, and more severe symptoms at baseline. We suggest that AIT is utilized early, possibly even as the initial treatment for AR. LRs might be a potential predictive factor for AIT responses. Highly symptomatic AR patients could get increased clinical responses to AIT. These findings help to better understand and perform AIT in our clinical practice.

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Author Contributions

Shanshan Qi, data collection, statistical analysis, and paper writing; Hao Chen, data collection, and statistical analysis; Nan Huang, supervising SCIT, data collection; Wenjing Li, supervising SCIT, data collection; Guanghui Liu, data collection; Yin Wang, performing SCIT; Lintao Hu, performing SCIT; Xiaolong Wang, performing SCIT; Wei Zhang, laboratory testing; Rongfei Zhu, supervising SCIT, data collection, paper writing, and revision.

Disclosure Statement

There were no conflicts of interest.

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