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Effects of subcutaneous immunotherapy in allergic rhinitis children sensitive to dust mites

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KEYWORDS
allergic rhinitis;
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Abstract
Background: Subcutaneous immunotherapy (SCIT) is now the only treatment that can modify the natural course of allergic rhinitis (AR). However, not all children with AR benefit from SCIT.
Objective: To evaluate the efficacy of SCIT in dust-mites-induced AR children and explore correlative factors predicting treatment response to SCIT.
Methods: 225 children aged 4–17 years old with AR were recruited from January 2016 to September 2019, and monitored at baseline, 4, 12, and 24 months after the start of SCIT treatment. The visual-analogue-score (VAS) was used to assess the clinical symptoms. Multivariate binary logistic regression analyses and receiver operating characteristic curves were used to explore correlative factors in predicting the efficacy of SCIT.
Results: The significant declines in VAS started after 4 months of SCIT and continued to improve throughout the study compared with baseline. An increase in children's age (OR=0.688, 95%CI: 0.479–0.988) and those with allergic history (OR=0.097, 95%CI: 0.009–1.095) were negatively associated with the risk of poor efficacy. Polysensitized children were more likely to suffer poor efficacy (OR=15.511 95%CI: 1.319–182.355). The clinical response at month 4 (r=0.707) and month 12 (r=0.925) was related to that at month 24. The area under the curve (AUC) for improvement at month 4 and month 12 was 0.746 and 0.860, respectively.
Conclusion: Our study confirmed the clinical efficacy of SCIT in AR children. Children with younger age, negative allergic history, and multiple allergens may predict a worse efficacy. The onset of action and the clinical response to SCIT in the second year can be predicted as early as by month 4.

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Introduction

Allergic rhinitis (AR) is one of the most common respiratory allergies, affecting 10%–40% of adults and 2%–25% of children worldwide.[1] In China, the prevalence of AR has been increasing constantly over the past few decades.[2] AR is usually characterized by the persistent or recurrent symptoms of sneezing, nasal itching, rhinorrhea, nasal obstruction, or a combination of these symptoms,[3] and has been proved to be a major risk factor for the development of asthma.[1] Children with AR have a higher prevalence of eustachian tube dysfunction, otitis media, and conductive hearing loss than the general pediatric population.[4] The symptoms and the associated comorbidities have an adverse impact on patients' sleep, cognition and memory, and may consequently influence the quality of life and adversely affect children's school productivity.[3,5] Considering its high prevalence and disease burden, AR may cause a substantial socioeconomic burden.

In China, the majority of AR patients are sensitized to house dust mites.[6] Treatment options for AR include the avoidance of allergens, pharmacologic therapy (including antihistamines, corticosteroids, and antileukotrienes), and allergen immunotherapy (AIT). Nevertheless, it is difficult to completely avoid house dust mite contact in real life. The first two can reach symptomatic relief but may be insufficient to control symptoms.[7, 8]

Allergen immunotherapy is an effective treatment for allergic rhinitis, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Several studies have reported that AIT can improve nasal and ocular symptoms and reduce the need for medications,[9] and it is the only treatment that can modify the natural course of the disease.[9] However, some patients do not respond effectively to SCIT.[10,11] Therefore, there is an urgent need for identifying correlative factors for the effect of SCIT in AR patients.

In this study, we prospectively explore the efficacy of SCIT and the relationship between children's clinical characteristics and the efficacy of SCIT in AR. For the prediction of patients' responses to SCIT in the second year, we used receiver operating characteristic (ROC) curves to determine the sensitivity, specificity, and predicted values for children's clinical parameters.

Materials and Methods

Study design and recruitment

Patients suffering from AR with or without asthma were recruited in the allergy clinic of The Children's Hospital Zhejiang University School of Medicine from January 2016 to December 2019. Subjects were sensitized only to dust mites or simultaneously sensitized to dust mites and other allergens (such as cat, dog dander, *Alternaria* sp, cockroach, and so on) according to the skin-prick test (SPT). They all fulfilled the criteria for the diagnosis of persistent AR based on the criteria in the WHO Consensus Statement on Allergic Rhinitis and its Impact on Asthma (ARIA).[12] Asthma was diagnosed based on Global Initiative for Asthma (GINA) guidelines.[13] All cases had unsatisfactory response to pharmacological treatment and were instructed to receive SCIT with allergen extract (Alutard Der p vaccine) for at least 36 months. None of the patients displayed contraindications to SCIT, according to the international guidelines.[14]

Face-to-face interviews were conducted with the children's parents before treatment, after the treatment at month 4, month 12, and month 24. Information on children's age, gender, allergens, history of eczema, and other allergic history (including food and drug), family allergic history, history of passive smoking, and keeping a pet or not were collected at their first visit. The visual analogue score (VAS) was used to assess the severity of children's symptoms.

The study was approved by the local Ethics Committee and informed consent was obtained from the guardian of each participant.

Skin-prick test

The SPT was performed by a trained allergist. Participants were instructed not to take any antihistamines or topical steroids for at least 72 h before the test. Standardized inhalant allergen extracts (Macro-Union Pharmaceutical, Beijing, China) were used for SPTs, including 19 allergens: dust mites (Dp and Dermatophagoides farina), cockroach, mulberry silk, animal dander (cat, dog, sheep, and horse), tree pollens (Sabina, Platanus, Populus, and cryptomeria), weed pollens (Artemisia, Ambrosia, and Humulus), and fungi (Alternaria, Cladosporium, Aspergillus, and Paecilomyces). Histamine (10 mg/mL) and diluent were used as positive and negative controls, respectively. The diameter of the wheal produced in response to a specific allergen was measured 15 min later. Then a skin index (SI = mean size of allergen wheal/size of histamine wheal) was calculated. The results were expressed in five grades according to SI: $0 < SI < 0.5$ = grade 1+, $0.5 \leq SI < 1$ = grade 2+, $1 \leq SI < 2$ = grade 3+, and $SI \geq 2$ = grade 4+. In the present study, the grade ≥2+ was considered positive.

Outcome measurement [visual analogue score (VAS)]

The VAS is recognized as a very useful tool to assess the subjective perception of the overall discomfort of AR for the last week. The score of each symptom varies from 0 (no symptoms) to 10 (most severe symptoms). Patients were asked to grade their symptoms retrospectively for the last week.[15]

Immunotherapy

All patients were treated by standardized SCIT with Alutard Der p vaccine. As described in our previous publication,[16] the SCIT treatment period comprised an initial build-up phase, followed by a maintenance phase according to the manufacturer's product insert. The build-up phase begins with an injection dose of 20 SQ units and increased weekly until a target maintenance dose of 100,000 SQ units (15-week up-dosing). Subsequently, the

patient followed maintenance injections every 6 weeks for 3 to 5 years at an injection dose of 100,000 SQ units. Every participant was observed at the clinic after each injection for at least 30 min for a possible side-effect of SCIT.

Statistical analysis

We first examined the demographic characteristics of the 225 participants and the overall characteristics of the VAS scores. Wilcoxon test was used to detect the difference in VAS scores at month 4, month 12, and month 24 of the treatment. Spearman correlation was used to examine the relationship between children's VAS scores at month 4, month 12, and month 24 of the treatment, respectively. Multivariate binary logistic regression analyses were used to determine the independent predicting factors for the SCIT clinical response. Based on a previous study, VAS is well validated for the measurement of AR symptoms.[17] VAS can be used relatively simpler and highly effective to assess disease control, and several previous researches on AR have used VAS as an evaluation tool.[17] Thus, in our study, the clinical response of SCIT was evaluated based on the reduction of VAS at month 4, 12, and 24 compared with the baseline. Effective SCIT at month 4, month 12, and the second year was defined as a 25% reduction in the VAS from baseline at month 4, month 12, and at end of the second year of immunotherapy, respectively. Otherwise, the SCIT was considered ineffective.[10, 11] The best cut-off values were determined based on their ROC curve, the area under the curve (AUC), sensitivity, specificity, and Youden index score.

All analyses were performed using Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston, MA, USA) and R software (http://www.R-project.org).

Results

Basic characteristics of the study population

A total of 225 patients aged 4–17 years were enrolled in this study. 104 patients were affected by rhinitis only, and 121 patients were affected by rhinitis combined with asthma. All children were sensitive to dust mites, among which 41.8% were having polysensitization. 23.6% and 27.1% of children had sinusitis and conjunctivitis, respectively, and all patients had no bronchitis within 2 weeks before enrollment and 3 days before each injection (Table 1). However, 15, 71, and 69 children dropped out during the first 4 months, 5–12 months, and the second year, respectively because of the long distance from the hospital, parents having no time, and heavy school work. In total, 210, 139, and 70 patients completed SCIT at 4th, 12th, and 24th month, respectively (Table 2).

Table 1 Baseline characteristics of patients (N=225).

Characteristics	Patients
Age (years) (mean ± SD)	8.9±2.6
Gender n(%); missing = 0	
Boy	150 (66.7%)
Girl	75 (33.3%)
Rhinitis/rhinitis + Asthma n(%)	
Rhinitis	104 (46.2%)
Rhinitis + Asthma	121 (53.8%)
Allergen n(%)	
Mono-sensitized (dust mites)	131 (58.2%)
Polysensitized (dust mites and others)	94 (41.8%)
Sinusitis n(%); missing = 22	
No	155 (76.4%)
Yes	48 (23.6%)
Conjunctivitis n(%); missing = 22	
No	148 (72.9%)
Yes	55 (27.1%)
Allergic history n(%); missing = 33	
No	118(61.5%)
Yes	74 (38.5%)
History of eczema n(%); missing = 33	
No	74 (38.5%)
Yes	118 (61.5%)
Passive smoking n(%); missing = 27	
No	123 (62.1%)
Yes	75 (37.9%)
Allergic history of family members n(%); missing = 24	
NO	82 (40.8%)
Yes	119 (59.2%)
Keeping pets n(%); missing = 62	
No	152 (93.3%)
Yes	11 (6.7%)

Table 2 Clinical response of SCIT at different treatment periods.

Clinical response	N (%)
Response at month 4 n(%); missing = 15	
Effective	112 (53.3%)
Ineffective	98 (46.7%)
Response at month 12 n(%); total missing = 86	
Effective	98 (70.5%)
Ineffective	41 (29.5%)
Response at month 24 n(%); total missing = 155	
Effective	54 (77.1%)
Ineffective	16 (22.9%)

Efficacy of SCIT at months 4, 12, and 24

The response to SCIT was considered effective in 112 (53.3%) patients at month 4 and 98 (70.0%) patients at month 12. SCIT was effective in 54 patients and ineffective in 16 patients at 24th month of the treatment. The overall efficacy rate of SCIT at the end of the second year was 77.1% (Table 2).

Significant declines were observed in VAS scores after 24 months of treatment compared to the baseline values (Figure 1). The significant declines in VAS scores started after 4 months of SCIT and continued to improve throughout the study compared with baseline.

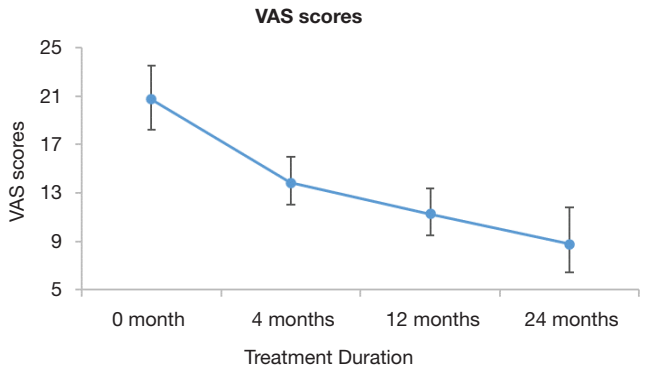

Figure 1 Changes in VAS scores before and after SCIT treatment. The significant declines in VAS scores started after 4 months of SCIT and progressed throughout the study compared with baseline (Wilcoxon test, all p value < 0.05). SCIT: Subcutaneous immunotherapy; VAS: Visual analogue score.

Univariate analysis

Children were mono-sensitized more likely to have a response to SCIT (Table 3). However, there was no difference between patients with and without an effective clinical response to SCIT in terms of age, gender, positive allergic history, family allergic history, and history of passive smoking (Table 3). Clinical response at month 4 ($r = 0.707$, $p < 0.001$), and month 12 ($r = 0.925$, $p < 0.001$) was strongly correlated with the clinical response at month 24 (Figure 2).

Multivariate analysis

Multivariate binary logistic regression analysis was used to determine the independent predicting factors for the clinical response to SCIT (Table 4). We found that an increase in children's age was negatively associated with the risks of treatment failure at month 24 after SCIT (OR = 0.688, 95%CI: 0.479, 0.988). Compared with mono-sensitized (dust mites), polysensitized children were more likely to suffer a worse efficacy (OR = 15.511, 95%CI: 1.319, 182.355). Better efficacy was observed among children with positive allergic history than those without allergic history (OR = 0.097, 95%CI: 0.009, 1.095) (marginally significant).

Figure 3 shows the sensitivity and specificity obtained by calculating ROC curves for the clinical responses at month 4 and month 12. The ROC areas under the curve were 0.746 (95%CI: 0.587, 0.905) for clinical responses at month 4 and 0.860 (95%CI: 0.745, 0.975) for clinical responses at month 12.

Discussion

Although the efficacy of SCIT on pediatric AR has been well documented, prospective researches focusing on the

Table 3 Predictive factors of clinical response to SCIT in the second year.

Factors[a]	Clinical response		*p*-value
	Effective (n = 54)[b]	Ineffective (n = 16)[b]	
Age (years) (mean ± SD)	10.5 ± 2.5	9.4 ± 2.0	0.129
Gender n(%)			0.826
Boy	39 (72.2%)	12 (75.0%)	
Girl	15 (27.8%)	4 (25.0%)	
Allergen kinds n(%)			0.025*
Mono-sensitized (dust mites)	37 (68.5%)	6 (37.5%)	
Ploy-sensitized (dust mites and others)	17 (31.5%)	10 (62.5%)	
Allergic history n(%)			0.588
No	23 (63.9%)	8 (72.8%)	
Yes	13 (36.1%)	3 (27.3%)	
Allergic history of family members n(%)			0.223
No	13 (31.0%)	6 (6%)	
Yes	29 (69.0%)	6 (6%)	
Passive smoking n(%)			0.838
No	22 (55%)	7 (58.3%)	
Yes	18 (45%)	5 (41.7%)	
Clinical response at month 4 n(%)			0.005*
Effective	28 (51.9%)	2 (12.5%)	
Ineffective	26 (48.1%)	14 (87.5%)	
Clinical response at month 12 n(%)			<0.001*
Effective	44 (81.5%)	2 (12.5%)	
Ineffective	10 (18.5%)	14 (87.5%)	

*$p < 0.05$.
[a]ANOVA was used for age, and Chi-squared test was used for gender, allergen kinds, allergic history, allergic history of family members, passive smoking, and clinical response at month 4 and month 12.
[b]Effective SCIT (subcutaneous immunotherapy) was defined as a 25% reduction in the VAS from baseline at the end of the second year of immunotherapy. Otherwise, the SCIT was considered ineffective.

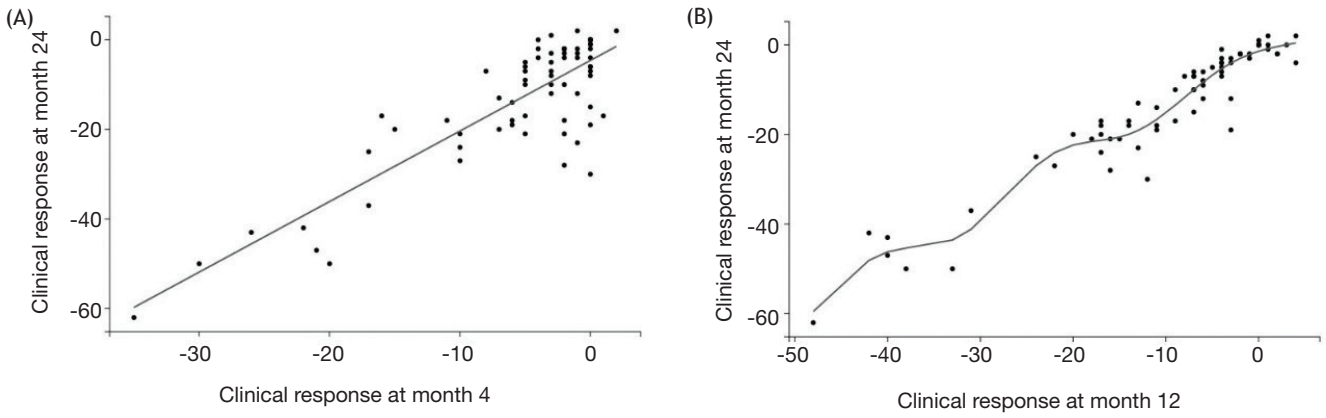

Figure 2 The relationship between clinical response (VAS scores) at month 4 (A), month 12 (B), and at month 24. We found that the clinical response at month 4 (Spearman correlation, $r = 0.707$, $p < 0.001$) and month 12 (Spearman correlation, $r = 0.925$, $p < 0.001$) were strongly associated with that at month 24 (the clinical response is the VAS of a patient after treatment minus VAS at baseline). VAS: Visual analogue score.

Table 4 Multivariate analysis for independently predicting factors for the clinical response to SCIT.[a]

Predicting factors	OR (95%CI)	*p*-value
Age	0.688 (0.479, 0.988)	0.042*
Gender		0.296
Boy	ref	
Girl	0.297 (0.031, 2.887)	
Allergen kinds		0.029*
Mono-sensitized (dust mites)	ref	
Polysensitized (dust mites and others)	15.511 (1.319, 182.355)	
Allergic history		0.059*
No	ref	
Yes	0.097 (0.009, 1.095)	
Allergic history of family members		0.480
No	ref	
Yes	0.523 (0.086, 3.160)	
Passive smoking		0.400
No	ref	
Yes	0.481 (0.087, 2.651)	
Eczema		0.594
No	ref	
Yes	1.635 (0.268, 9.964)	

*$p<0.05$ or was marginally significant.
[a]Effective SCIT (subcutaneous immunotherapy) was defined as a 25% reduction in the VAS from baseline at the end of the second year of immunotherapy. Otherwise, the SCIT was considered ineffective.

predictive factors for clinical response to SCIT are fewer. Our results suggest that SCIT is effective in reducing symptoms of AR. SCIT is more effective in mono-sensitized children, older children, and those with positive allergic history. The onset of action and the clinical response to SCIT in the second year can be predicted as early as month 4.

Consistent with previous studies,[6,18,19] our study showed patients' clinical symptoms alleviated and their quality of life improved after receiving SCIT. SCIT could induce immune tolerance to allergens for AR patients.[20] The SCIT-induced immune response is mainly mediated by the generation of Treg and Breg cells, which were associated with an increase in IL-10 and TGF-β.[21,22] IL-10 and TGF-β could suppress both the activity and proliferation of Th2 cells, and then inhibit the production of Th2 cytokines (IL-4, IL-5, IL-9, IL-13), consequently reducing the function and activation of eosinophils, basophils, mast cells, and IgE-secreting B lymphocytes.[23-26] However, there is no specific biomarker for monitoring clinical benefit on an individual patient level to date. Further studies need to be conducted to identify and confirm biomarkers suitable for SCIT efficacy monitoring and recognizing potential responders and non-responders.

In China, polysensitization is much more prevalent than monosensitization for patients with allergic diseases.[27] The comparison of the efficacy of SCIT between mono-sensitized and polysensitized patients remains inconclusive. Some previous studies showed that mono-sensitized and polysensitized adult patients showed equal improvement in symptom scores, VAS scores, and quality of life,[27-30] whereas others found that mono-sensitized patients may benefit more from SCIT.[31] Our study found that mono-sensitized children are more likely to have an effective response compared to polysensitized children. This may be explained by the fact that the mono-sensitized patients had a higher ratio of Der f sIgE/tIgE and Der p sIgE/tIgE, which was proved to be associated with an effective response to SCIT.[31,32] However, the specific mechanisms are still unclear.

It is now generally accepted that performing SCIT at an early age might be more beneficial for children with AR because the immune system may respond better to the treatment when it is still under development.[33] However, our study found that increase in children's age is negatively associated with risks of poor efficacy. SCIT improves clinical symptoms in AR children by shifting the Th2 secretory profile to a Th1 cytokine pattern.[34] We assume that the balance of Th1/Th2 among younger children may be recovered more slowly than that among older children.[35] Age seems to have a certain effect on the onset time of SCIT treatment, but the role of age in the long-term effect of SCIT on pediatric AR needs to be further studied. It

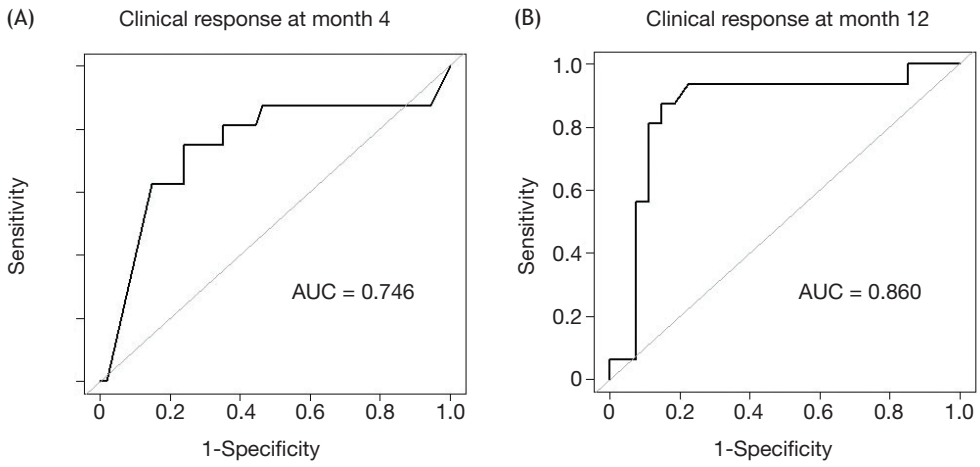

Figure 3 ROC curves obtained with the clinical response at month 4 (A) and month 12 (B) by plotting sensitivity in patients with an effective response to SCIT versus 1-specificity in patients with an ineffective response to SCIT. ROC areas under the curve (AUC) for month 4 (sensitivity 75.0% and specificity 75.9%) and month 12 (sensitivity 87.5% and specificity 85.2%) improvement percentages are 0.746 and 0.860, respectively.
ROC: Receiver operating characteristic; SCIT: Subcutaneous immunotherapy.

might also be due to the small sample size (n = 70) in the second year, which may limit the statistical power of the findings.

Our study is one of the fewer to reveal that children with allergic history do have particular benefits from SCIT over those without allergic history. The underlying mechanism is still unclear. We speculate that children with allergic history may have a higher initial level of sIgE, and those children may benefit more from SCIT.[36,37] However, inconsistent with one previous study,[11] we failed to demonstrate a significant relationship between tobacco smoke exposure, family history of allergic disease, and the therapeutic effect of SCIT. Cigarette exposure is associated with airway obstruction and slowed the growth of lung function in children and adolescents, which would reduce the effectiveness of SCIT.[11] While one previous study found that children or adolescents who smoke less than five cigarettes/day were insignificantly related to the pulmonary function.[38] We speculate that the participants in our study were not exposed to tobacco smoke for a long time, and the structure and function of the lungs have not been damaged.[11] We found that positive family history of allergic disease was not an independent factor for ineffective clinical response to SCIT. Eosinophils and allergic diseases are closely related,[39] but no correlation between blood levels of eosinophils and the clinical response to AIT was found in any previous studies.[11]

Our study is consistent with other studies finding that the onset of action of SCIT can be predicted as early as month 4.[10,40] When comparing the time of onset of clinical effect with associated immunological changes, previous studies found that SCIT could elicit a simultaneous surge in the production of TGF-β from month 1 and IFN-γ, IL-10, IL-13, and the blocking IgG antibodies at month 4.[40-42] We also found that the clinical response to SCIT in the second year can be predicted as early as month 4. SCIT is a long-duration therapy, and at least 3 to 5 years duration was recommended to achieve the best clinical benefits.[43,44] Although SCIT is a very effective treatment, not all patients benefit from treatment. Some patients might drop out because of poor efficacy.[10] Our findings may help determine those patients who might best benefit from this therapy and if it is necessary to continue. We also suggested that clinicians should monitor the clinical response at the early stage of treatment using the symptom score to evaluate and predict the efficacy of SCIT.[10]

There are some limitations in our study. First, it was an open observational study without placebo control. Second, some children dropped out of this study and only 210, 139, and 70 patients completed SCIT at 4, 12, and 24 months, respectively, which may induce a bias in the findings. Third, only VAS was evaluated as an evaluation index of efficacy. Fourth, we failed to collect accurate serum sIgE levels. However, we believe that these limitations do not significantly influence the main findings of our study.

Conclusions

In conclusion, SCIT does have a positive effect on children's symptoms, and the efficacy of SCIT in the second year can be predicted as early as month 4. Younger age, multiple allergens (dust mites and others), and negative allergic history are inclined to suffer a worse clinical response to SCIT. These results provide useful information for taking novel treatment strategies for AR.

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Conflicts of Interest

All authors declare no conflicts of interest.

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