ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
February 2024; 23(1):52-58.
DOI: 10.18502/ijaai.v23i1.14953

Baseline Severity and Disease Duration Can Predict the Response to Allergen-specific Immunotherapy in Allergic Rhinitis

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Received: 15 September 2023; Received in revised form: 6 October 2023; Accepted: 14 October 2023

ABSTRACT

Allergen-specific immunotherapy (AIT) has confirmed its efficacy in improving the symptoms of allergic rhinitis. However, no reliable biomarkers have been identified to predict the efficacy of AIT were found. We aimed to find clinical and immunological markers to predict efficacy in children after 2 years of sublingual immunotherapy (SLIT).

A total of 285 children diagnosed with allergic rhinitis were recruited. The clinical efficacy was evaluated by comparing endpoint and baseline symptom and medication scores (SMS). Baseline clinical and immunological markers (serum total and specific immunoglobulin [Ig]E) and their correlation with clinical efficacy were analyzed.

Of the 285 children recruited, 249 completed the 2-year SLIT program. After 2 years of SLIT, 68.3% of the children showed a significant response. Children in the Remarkable Response Group had the highest baseline SMS and most extended disease duration, followed by the Effective Relief and Unresponsive Group. Correlation analysis demonstrated that SMS improvement was positively correlated with baseline SMS (r=0.67) and disease duration (r=0.35). SMS improvement was not correlated with age, body mass index, total or specific IgE levels, or their ratios.

Our results show that baseline SMS and disease duration can predict the efficacy of SLIT. Our study can guide the selection of suitable candidates for SLIT.

Keywords: Allergic rhinitis; Sublingual immunotherapy

INTRODUCTION

Allergic rhinitis (AR), a chronic inflammatory upper airway disease, has a prevalence of up to 20% in children worldwide.[1] Allergen-specific immunotherapy (AIT) has been applied for the treatment of AR for almost a century because AIT can modify the disease progression and reduce the occurrence of new sensitization.[2]

Accumulating evidence has confirmed that both subcutaneous immunotherapy (SCIT) and sublingual

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immunotherapy (SLIT) alleviate symptoms and decrease drug usage significantly.[3–5] As for safety, SLIT causes far less severe adverse reactions than conventional SCIT.[6] Most adverse reactions of SLIT were reported locally, while moderate or severe adverse reactions were found only in very few cases.[6]

The identification of biomarkers that can predict response to AIT treatment in AR patients is important for patient selection. Researchers have always been trying to find reliable biomarkers for predicting the efficacy or safety of AIT. However, no consensus has been reached so far. Several studies have reported that serum total or specific immunoglobulin E (tIgE or sIgE) or the sIgE/tIgE ratio can predict the clinical response to AIT in children and can be used for patient selection before treatment.[7,8] On the contrary, a randomized controlled study found no correlation between the IgE ratio and clinical response to AIT.[9]

In the present study, we aimed to find potential clinical and immunological markers for predicting the clinical efficacy of SLIT in children.

MATERIALS AND METHODS

Patients and Treatment

We recruited 285 children with AR (4 to 14 years old) from February 2019 to February 2020 who were referred to our center. The inclusion criteria were listed as follows: 1) at least one year of typical nasal symptoms, 2) positive allergen test only to house dust mite confirmed by skin prick test or sIgE, and 3) poor response to usual anti-anaphylactic treatment. Children were excluded if they had other allergic diseases or severe systematic diseases. The study was approved by the local Ethics Committee (No. 261A01), and informed consent was obtained from the patients' parents.

Dermatophagoides farinae (Der f) drops (Wolwopharma, China) were applied to the patients with increasing doses from 1 μg/mL (0.05 μg) to 100 μg/mL (50 μg) every day in the first 3 weeks and 333 μg/mL (50 μg) once daily in the maintenance period, according to the manufacturer's instructions. The children were instructed to maintain the drops under the tongue for 1 to 3 minutes. The adverse reactions were recorded during the treatment.

Evaluation of SLIT Efficacy and Safety

Clinical efficacy was determined by calculating the improvement of nasal symptoms and medication scores after the 2-years SLIT. Daily nasal symptoms (i.e., runny, itchy, or stuffy nose and sneezing) were scored between 0 for no symptoms and 3 for severe symptoms. Daily drug use was scored as 1 point for oral or nasal antihistamines and 2 points for intranasal corticosteroids. Symptom medication score (SMS) was obtained by adding up the above two average scores.[10] According to the improvement degree of SLIT, children were grouped as a remarkable response group (>51%), an effective Relief group (21-50%), and an Unresponsive group (<20%).[11] The criteria for categorizing adverse reactions were according to the grading system for SLIT-associated adverse events (AEs) as described in the Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma.[11] In brief, when no symptomatic treatments were required, AEs were classified as mild; when symptomatic treatment was needed without discontinuation of SLIT, they were defined as moderate; and when SLIT was discontinued, the AEs were defined as severe.

Immunological Markers

The serum tIgE and sIgE were measured by the Unicap system (Phadia, Sweden) at baseline level and 2 years after the initiation of SLIT.

Statistical Analysis

Statistical analyses were done using SPSS 17.0. The nonparametric Mann-Whitney U test and Bonferroni post hoc analysis were conducted to adjust for multiple comparisons. Correlations were assessed by the Spearman rank correlation analysis. A p level < 0.05 was defined as statistically significant.

RESULTS

Baseline Characteristics of Subjects

We recruited 285 children, and 249 completed the 2 years of treatment (Table 1). After 2 years of treatment, 36 children discontinued participation in our study due to the lack of efficacy in 4 cases, adverse events in 1 case, failure to adhere to treatment in 18 cases, and loss to follow-up in 13 cases. There was no significant difference in characteristics at baseline between the 2 groups. Among the children who finished the treatment period, 5 moderate AEs and 7 severe AEs were reported (Table 2).

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Clinical Efficacy and Related Factors

After the therapy, 68.3% of the patients experienced a significant improvement. SLIT was effective in 21.3% of the patients and not effective in 10.4% (Table 3). Furthermore, the SMS score in the remarkable effect group and effective group decreased significantly compared to the baseline scores (Table 3) (Figure 1).

We found that baseline SMS scores and disease duration were significantly different among groups. The remarkable effect group had the highest baseline SMS score and longest disease duration, followed by the effective group and ineffective group (Table 4). Children in the remarkable effect group were older than those in the effective group (Table 4).

Correlation analysis demonstrated that SMS improvement was not correlated with age, body mass index, tIgE levels, sIgE levels, or sIgE/tIgE ratios. SMS improvement was positively correlated with baseline SMS and disease duration (Table 5).

Our ROC analysis of the baseline SMS showed that a score of greater than 5.5 had the best sensitivity (72.1%) and specificity (64.5%) to predict SMS improvement. Disease duration longer than 3.5 years had the best sensitivity (66.9%) and specificity (91.2%) to predict SMS improvement (Figure 2).

Table 1. Baseline characteristics of study subjects

Groups	Subjects who completed the study	Subjects who dropped out of the study
Cases	249	36
Age (years)	8.1±4.5	9.3±3.58
Male/female	145/104	20/16
Body mass index	18.9±4.1	18.2±4.6
Duration of symptoms (years)	2.3±1.3	1.8±1.6
tIgE (IU/mL)	513.1±428.9	375.2±216.5
Serum sIgE level to Derf (IU/mL)	31.7±46.5	45.2±32.2
Serum sIgE level to Derp (IU/mL)	29.6±35.5	23.4±29.1

Data presented as mean ± standard deviation (SD).

Table 2. Adverse reactions during the treatment period

Adverse reactions	Numbers
Mild	0
Moderate	5
Severe	7
Total	12

Table 3. Clinical efficacy of SLIT after 2 years of treatment

	Remarkable effect group	*p*	Effective group	*p*	Ineffective group	*p*
Baseline						
Cases	170 (68.3%)		53 (21.3%)		26 (10.4%)	
Symptom score	6.5±2.1		5.1±1.9*	0.01	2.6±1.5*#	0.001
Medication score	2.3±0.4		2.3±0.7		3.3±1.2*#	0.002*/0.01#
Symptom and medication scores	9.9±2.7		7.9±2.8*	0.02	6.4±2.1*#	0.01*/0.012#
After Therapy						
Cases	170 (68.3%)		53 (21.3%)		26 (10.4%)	
Symptom score	1.2±0.9$	0.01	2.2±1.7*$	0.01/0.02	3.5±1.1*#	0.02*/0.01#
Medication score	0.7±0.5$	0.002	0.9±0.4$	0.002	1.8±0.6*#	0.003*/0.01#
SMS scores	2.2±0.7$	0.03	3.1±1.8*$	0.02/0.01	5.4±1.3*#	0.02*/0.04#

Data presented as mean and standard deviation.

* Compared with the remarkable effect group, $p<0.05$. # Compared with the effective group, $p<0.05$.

$ Compared with baseline level, $p<0.05$.

Table 4. Comparison of baseline characteristics among groups

	Remarkable effect group	Effective group	Ineffective group
Cases	170 (68.3%)	53 (21.3%)	26 (10.4%)
Age	7.8±3.7	8.6±2.9*	8.8±3.1
Sex (male/female)	98/72	28/25	19/7
Body mass index	19.4±3.3	18.7±4.1	18.5±4.6
Disease duration	2.5±1.4	1.7±0.8*	1.1±0.6*#
Total IgE	534.0±415.7	436.5±317.2	365.1±299.3
sIgE to Derp	32.4±21.3	29.6±21.3	26.8±22.1
sIgE to Derf	39.6±24.5	31.8±26.7	31.6±21.8
Derp + Derf	61.4±56.0	63.8±27.5	59.8±32.8
sIgE/tIgE	0.4±0.2	0.3±0.2	0.3±0.3
Baseline SMS score	9.9±2.7	7.9±2.8*	6.4±2.1*#
Adverse reactions	7(4.1%)	3(5.6%)	2(7.6%)

Data presented as mean and standard deviation.

* Compared with remarkable effect group, $p<0.05$. # Compared with effective group, $p<0.05$.

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Table 5. Relationship between related factors and symptom-medication score (SMS) improvement

	SMS improvement	
	r	***p***
Age	-	0.37
Body mass index	-	0.06
Disease duration	0.35	0.01
Baseline SMS	0.67	0.001
Total IgE	-	0.34
sIgE to Derp	-	0.45
sIgE to Derf	-	0.39
Derp + Derf	-	0.55
sIgE/tIgE	-	0.23

SMS: symptom and medication scores.

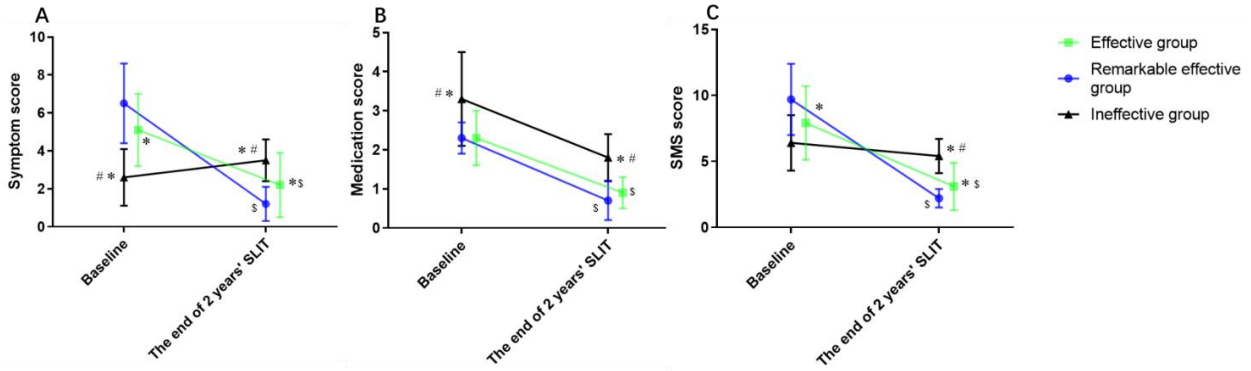

Figure 1. The change of symptom score, medication score, and symptom-medication score (SMS) after two years of SLIT. *Compared with remarkable effect group, $p<0.05$. #Compared with effective group, $p<0.05$. $Compared with baseline level, $p<0.05$.

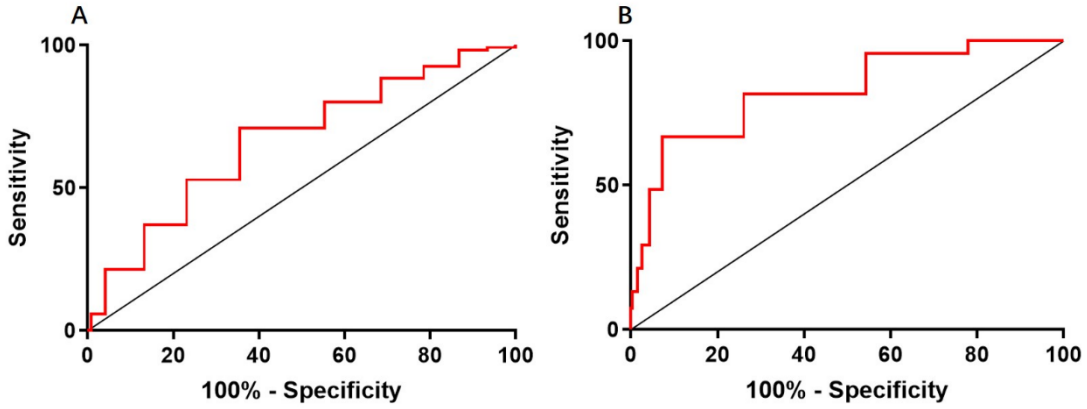

Figure 2. ROC analysis of the baseline SMS showed that a score of greater than 5.5 had the best sensitivity (72.1%) and specificity (64.5%) to predict SMS improvement (A). Disease duration longer than 3.5 years had the best sensitivity (66.9%) and specificity (91.2%) to predict SMS improvement (B).

DISCUSSION

AIT is the only treatment that can modify the natural process of IgE-mediated diseases. Many studies have been performed to determine the efficacy of AIT, but the predictors for the clinical response to AIT are limited and controversial.

The tIgE and sIgE are the two most widely studied indicators with inconsistent results. Di Lorenzo and Gulbin's study suggested that the clinical response was correlated with the serum sIgE/tIgE ratio.[7] Li et al. suggested that the serum tIgE can predict the clinical efficacy of SIT in allergic asthma and rhinitis.[12] Ciprandi and Lee et al. demonstrated that high sIgE levels can predict the clinical response of AIT.[13,14] However, Fujimura's report found that subjects with a low serum sIgE/tIgE ratio received better responses compared with subjects with a higher ratio.[15] Our previous study showed that sIgE and the sIgE/tIgE ratio can be used to predict the short-term response of SLIT in children.[16] In the present study, our data showed that sIgE, tIgE, and sIgE/tIgE were not correlated with clinical response after 2 years of SLIT. Since all children in our study were allergic to *Dermatophagoides pteronyssinus* (Der p) and/or Der f, we also analyzed whether the sum of sIgE against Der p and sIgE against Der f and the ratio of sum with tIgE can predict the efficacy of SLIT. Our results found that these parameters were not correlated to the response of SLIT. We also noticed that the change in IgE levels had no fixed trend during the treatment period. Previous studies have found that AIT often caused an initial increase in serum sIgE and a gradual decrease as treatment continued. However, the decrease in IgE levels was not significantly correlated with clinical response.[17]

Previous studies have also investigated the clinical biomarkers for predicting the efficacy of AIT. However, none of them has found a correlation between effectiveness and age, baseline symptoms, and disease duration. Our present data showed that baseline SMS and disease duration were correlated with the efficacy of AIT. Children with higher baseline symptoms and longer disease duration will benefit more improvement from a 2-year treatment. Two reasons may explain these results. First, the improvement of SMS may be more easily felt by children with higher baseline symptoms. Second, children with higher baseline symptoms and longer disease duration may be more focused on during treatment, and compliance may be better. Interestingly, we also found that children in the remarkable effect group were older than those in the effective group, which the better compliance of older children may explain.

Overall, the above information informs us that when including children with lower SMS, short disease duration, or young age, it is essential to ensure adequate communication with parents before starting SLIT. Additionally, parents should be fully informed about the possibility of a poor response to SLIT.

Our study had some limitations. Firstly, biases such as treatment duration, study population (pediatrics vs. adults), or sample selection can affect our results. Secondly, multicenter studies with large sample sizes were needed to confirm our data further. Thirdly, our data apply only to children.

In summary, our results proved that children with higher baseline SMS, longer disease duration, and older age may benefit more from SLIT. Our study guides the selection of suitable candidates for SLIT.

STATEMENT OF ETHICS

The study was approved by the Ethics Committee (No. 261A01) of Guangzhou Women and Children's Medical Center and informed consent was obtained from the patients' parents.

FUNDING

This study was funded by grants from the National Natural Science Grant of China (No. 81970861), the Guangdong Province Natural Science Grant (No. 2021A1515010940), and the Science and Technology Program of Guangzhou (No. 202102020079).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the children and their parents for participating in the study.

REFERENCES

1. Bousquet J, Melén E, Haahtela T, Koppelman GH, Togias A, Valenta R, et al. Rhinitis associated with asthma is

distinct from rhinitis alone: The ARIA-MeDALL hypothesis. Allergy. 2023;78(5):1169-203.
2. Gradman J, Halken S. Preventive Effect of Allergen Immunotherapy on Asthma
and New Sensitizations. J Allergy Clin Immunol Pract. 2021;9(5):1813-7.
3. Penagos M, Durham SR. Allergen immunotherapy for long-term tolerance and prevention. J Allergy Clin Immunol. 2022;149(3):802-11.
4. de Blay F, Gherasim A, Casale TB, Doyen V, Bernstein D. Which patients with asthma are most likely to benefit from allergen immunotherapy? J Allergy Clin Immunol. 2022 Mar;149(3):833-43.
5. Jin Youp Kim, Myoung-Jin Jang, Dong-Young Kim, Seok-Won Park, Doo Hee Han. Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis-Based Comparison. J Allergy Clin Immunol Pract. 2021;9(12):4450-58.e6.
6. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. Curr Opin Allergy Clin Immunol. 2013;13(6):656-62.
7. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol. 2009;123(5):1103-10, 10.e1-4.
8. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. J Allergy Clin Immunol Pract. 2014;2(3):300-5.
9. Würtzen PA, Lund G, Lund K, Arvidsson M, Rak S, Ipsen H. A double-blind placebo-controlled birch allergy vaccination study II: correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation. Clin Exp Allergy. 2008;38(8):1290-301.
10. Pascal Demoly, Jonathan Corren, Peter Creticos, Frédéric De Blay, Philippe Gevaert, Peter Hellings, et al. A 300 IR sublingual tablet is an effective, safe treatment for house dust mite-induced allergic rhinitis: An international, double-blind, placebo-controlled, randomized phase III clinical trial. J Allergy Clin Immunol. 2021;147(3):1020-1030.e10.
11. Chinese Collaborative Group on Allergic Rhinitis Research. Expert Consensus on Subcutaneous Immunotherapy for Allergic Rhinitis 2015. Chinese J Otolaryngology Head and Neck Surgery. 2015;22(8):379-404.
12. Li Q, Li M, Yue W, Zhou J, Li R, Lin J, et al. Predictive factors for clinical response to allergy immunotherapy in children with asthma and rhinitis. Int Arch Allergy Immunol. 2014;164(3):210-7.
13. Ciprandi G, Silvestri M. Serum specific IgE: a biomarker of response to allergen immunotherapy. J Investig Allergol Clin Immunol. 2014;24(1):35-9.
14. Lee JH, Kim SC, Choi H, Jung CG, Ban GY, Shin YS, et al. A Retrospective Study of Clinical Response Predictors in Subcutaneous Allergen Immunotherapy With House Dust Mites for Allergic Rhinitis. Allergy Asthma Immunol Res. 2018;10(1):18-24.
15. Fujimura T, Yonekura S, Horiguchi S, Taniguchi Y, Saito A, Yasueda H, et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. Clin Immunol. 2011;139(1):65-74.
16. Liu W, Zeng Q, Luo R. Predictors for Short-Term Efficacy of Allergen-Specific Sublingual Immunotherapy in Children with Allergic Rhinitis. Mediators Inflamm. 2020;2020:1847061.
17. Sindher SB, Long A, Acharya S, Sampath V, Nadeau KC. The Use of Biomarkers to Predict Aero-Allergen and Food Immunotherapy Responses. Clin Rev Allergy Immunol. 2018;55(2):190-204.