

Risk Factors for Safety of Allergen-Specific Sublingual Immunotherapy in Children with Allergic Rhinitis

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Keywords

Sublingual immunotherapy · Allergic rhinitis · Efficacy · Safety · Adverse events

Abstract

A good compliance often attributes to good efficacy and safety of sublingual immunotherapy (SLIT). However, few studies have been conducted on the safety of SLIT treatment in children. We aimed to confirm the pretreatment parameters to predict the safety in children who underwent SLIT. 601 children with allergic rhinitis (AR) treated with SLIT were enrolled in this study. Baseline clinical information and laboratory parameters were collected. The clinical response and adverse events (AEs) were recorded and evaluated. A multivariate logistic regression model was established to confirm the predictors for AEs. The AEs were reported in 75 children (13.8%). The serum-specific IgE (s-IgE) level was significantly correlated with the occurrence of AEs by multivariate logistic regression analysis. Our receiver operating characteristic (ROC) analysis of the serum s-IgE levels >21.6 IU/mL had the best sensitivity (83.7%) and specificity (76.7%) to predict safety. The serum s-IgE level was significantly correlated with safety of SLIT in children, which may be helpful for patient selection before SLIT.

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Introduction

Allergic rhinitis (AR) is a common chronic respiratory disease worldwide, affecting about 20% of the children, and its prevalence tended to increase gradually [1]. Allergy immunotherapy (AIT) is the only method which can modify disease progression and result in decreased pharmacotherapy use and maintain treatment effects even after treatment [2]. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been proved to be effective and safe by previous studies [3–5]. SLIT is more acceptable for children since it has fewer and less severe adverse events (AEs) compared with conventional SCIT [6]. Most reported AEs occurred in the oral mucosa and/or digestive system, while moderate/severe AEs were reported only in a few cases. Therefore, some children discontinue or reject SLIT despite of good efficacy.

A poor compliance is a general problem in SLIT. On the contrary, a good compliance often attributes to good efficacy and safety of SLIT. However, few studies have been conducted on the safety of SLIT treatment in children [7]. Therefore, identifying predictors for AEs in SLIT is of great significance. With these predictors, doc-

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tors can pay more attention to patients who are more likely to have AEs; thus, the SLIT safety and compliance could be significantly enhanced.

In this study, we evaluate the efficacy and safety of children who underwent SLIT. The clinical characteristics and laboratory parameters were analyzed for the prediction of AEs, and receiver operating characteristic (ROC) curves were used to determine the sensitivity, specificity, and predicted values for target predictors.

Methods

Patients

A total of 601 children with AR treated with SLIT between January 2017 and October 2018 in the Department of Otolaryngology, Guangzhou Women and Children's Medical Center, were recruited in this study. The AR was confirmed as described in ARIA [8]. The typical symptoms and disease duration were recorded. The allergy was determined by the prick test or specific IgE (s-IgE) for common allergens. We excluded the children allergic to other allergens except for dermatophagoides farinae (Der f). The exclusion criteria included asthma, atopic dermatitis, or other systematic diseases. The study was approved by the local ethics committee, and the written informed consent was obtained. Baseline characteristics such as sex, age, parental allergic history, passive smoke history, daily diet, living environment, physical activity, disease duration, and severity were collected at the enrollment.

Sublingual Immunotherapy

SLIT was performed as previously described [9]. The Der f drops (Wolwopharma Biotechnology Co., Zhejiang, China) were given with increasing doses (No. 1, 1 µg/mL; No. 2, 10 µg/mL; No. 3, 100 µg/mL) during 3 weeks' build-up stage and increased to 333 µg/mL (No. 4) once daily during the maintenance stage. The drops were given sublingually for 2–3 min before swallowing.

Symptom and Medication Score and Evaluation of Efficacy

The symptom and medication scores were recorded at baseline and 12 months after the beginning of SLIT. The nasal symptoms (runny nose, sneezing, blocked nose, and itchy nose) were scored as follows: 0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, and 3 = severe symptoms.

The oral or nasal antihistamines and/or intranasal steroids were allowed to be taken in case of aggravated symptoms. The medication score was defined as follows: 1 point for an antihistamine tablet, intranasal antihistamine; 2 points for an intranasal corticosteroid as described in the statement of the World Allergy Organization Task Force. The symptom and medication scores were summed, and a combined Symptom Medication Score (SMS) was obtained by adding together the 2 scores. The children who obtained at least a 30% SMS decrease compared with their baseline score after 1-year SLIT were classified into the effective group, and others were classified into the ineffective response group.

Assessment of AEs

AEs were assessed as related or unrelated to SLIT by on-site visits and telephone calls. All AEs occurred locally, and no serious AEs

Table 1. Baseline characteristics of 601 children who underwent SLIT

Age, years, mean±SEM	8.1±3.1
Male/female	319/282
Duration of symptoms, years	3.8±1.5
Serum s-IgE level to Der f, IU/mL*	33.6 (4.1–76.9)
Serum s-IgE/t-IgE ratio*	17.8 (8.3–36.1)
Response to SLIT	341/601

SLIT, sublingual immunotherapy; s-IgE, specific IgE; Der f, dermatophagoides farinae; t-IgE, total IgE. * Geometric mean after logarithmic transformation (95% CI).

were reported in this study. The AEs were classified as aggravation of allergic symptoms (runny nose, sneezing, blocked nose, itchy nose, and cough), local irritation symptoms (lip swelling or edema, palatal edema, swollen tongue or edema, pharyngeal edema or throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus), gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea), and other symptoms (chest tightness and headache).

Laboratory Parameters

Peripheral blood cell counts were determined by using a Technicon-H1 blood cell counter (Bayer, Leverkusen, Germany). The serum total IgE (t-IgE), eosinophil cationic protein (ECP), and s-IgE were tested by using a Unicap ECP kit (Pharmacia Diagnostics, Uppsala, Sweden) at baseline level.

The concentrations of cytokines were measured by using ELISA kits (R&D systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The sensitivity for cytokines was as follows: IL-4, 0.22 pg/mL; IL-5, 3.9 pg/mL; IL-12, 5 pg/mL; IL-13, 125 pg/mL; IL-17, 62.5 pg/mL; IL-10, 62.5 pg/mL; IL-35, 62.5 pg/mL; IFN-γ, 8 pg/mL; TGF-β, 125 pg/mL.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0. Data were presented as the mean and 95% confidence interval (CI) for the mean. The 2-sided *t* test was carried out for group comparison. The χ^2 test was performed to compare categorical variables.

The multivariate unconditional logistic regression model was established to identify the independent predicting factors for the safety of SLIT. The results were presented as odds ratios (ORs) and their 95% CIs. For all tests, *p* < 0.05 was considered statistically significant. A ROC curve was also established to confirm the cutoff values of s-IgE levels. The area under curve (AUC) was used to assess the result of the ROC curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the corresponding cutoff values of s-IgE were calculated.

Results

Clinical Efficacy of SLIT

This study included 601 children, and the baseline characteristics are summarized in Table 1. During the

Table 2. The reasons for the dropout of 59 children during SLIT

Reasons	<i>n</i>
Lack of efficacy	19
Adverse events	11
Fail to take medication according to schedule	12
Lost of follow-up	17
<i>n</i>	59
SLIT, sublingual immunotherapy.	

Table 4. AEs during SLIT

AEs	<i>n</i>	Time to onset	Duration of AEs
Allergic symptoms	26	1–22 days	2–7 days
Local irritation symptoms	25	1–14 days	2–3 days
Gastrointestinal symptoms	14	1–8 days	1–3 days
Other minor symptoms	10	1–10 days	1–3 days
<i>n</i>	75		

SLIT, sublingual immunotherapy; AEs, adverse events.

1-year treatment, 59 children dropped out the study due to different reasons (Table 2). As shown in Table 3, the average symptom and medication score after 1-year treatment in the effective group decreased significantly compared with the ineffective group.

The Characteristics of AEs

The AEs were reported in 75 children (13.8%). The time to onset of AEs ranged from 1 day up to 22 days. The duration of local AEs is reported in Table 4.

The aggravation of allergic symptoms was found in 26 children, local irritation symptoms in 25 children, gastrointestinal symptom in 14 children, and other symptoms (chest tightness and headache) in 10 children. We also found that the occurrence of AEs was comparable between effective and ineffective groups ($p > 0.05$).

Comparison between Patients with and without AEs in SLIT

Between patients with and without AEs during 1-year SLIT, we found that serum t-IgE levels, serum s-IgE levels, blood eosinophil percent, and blood eosinophil count were correlated with the occurrence of AEs (Table 5).

Table 3. Clinical efficacy after 1-year SLIT treatment

	Effective group	Ineffective group
Cases	341 (63%)	201 (37%)
End-point symptoms	2.4±1.3*	6.7±2.9
End-point medication	3.1±1.8*	6.8±3.1
SMS	6.2±2.1*	11.8±4.5

SLIT, sublingual immunotherapy; SMS, Symptom Medication Score. Data are presented as median values (minimum-maximum). * Compared with the ineffective group, $p < 0.05$.

Multivariate Analysis

Multivariate logistic regression analysis showed that the occurrence of AEs was significantly correlated with serum s-IgE levels and blood eosinophil percent (Table 6). However, blood eosinophil percent OR has no relevance as CI includes 1 value. Therefore, we only determined the clinical implication of serum s-IgE levels for the prediction of AEs of SLIT. The AUC was 0.83 for serum s-IgE levels (95% CI: 0.764–0.896) (Fig. 1). Our ROC analysis of the serum s-IgE levels >21.6 IU/mL had the best sensitivity (83.7%) and specificity (76.7%) to predict the occurrence of AEs. The positive predictive value and negative predictive value were 0.25 (95% CI: 0.14–0.29) and 0.95 (95% CI: 0.91–0.99), respectively.

Discussion

The efficacy of SLIT has been confirmed in previous studies [4]. However, the occurrence of AEs often contributes to dropout and poor compliance during SLIT. Therefore, it would be helpful to search for predictors to identify those children who might have AEs during SLIT.

In the present study, all reported AEs occurred locally and no serious AEs were found. The main type of AEs included aggravation of allergic symptoms, local irritation symptoms, gastrointestinal symptoms, and other symptoms.

Consistently, Cox summarized 66 clinical studies on SLIT and no serious life-threatening reactions were found. As for China, no serious AEs of SLIT have been reported [10]. Shao reported fifty-four AEs in 39 children aged 3–13 years with respiratory allergies treated with SLIT [11]. Most of the AEs were of grade 1, and no severe systemic AEs were found. Lin confirmed the safety and efficacy of SLIT in young AR children (<4 years old) [12]. In sum, most reported AEs were mild and occur in the

Table 5. Univariate logistic analysis of factors associated with safety of SLIT

Characteristic	Groups		<i>p</i> value
	AE group	no AE group	
Subjects, <i>n</i> (%)	75 (13.8)	467 (86.2)	0.003
Age, years	7.8 (5–12)	7.9 (5–12)	0.256
Male, <i>n</i> (%)	41 (55)	262 (56)	0.178
BMI	22.6 (18.1–25.3)	23.1 (18.2–24.5)	0.377
Diet habits, %			
Seafood	18.9	19.8	0.173
Poultry	47.6	45.6	0.235
Pork	81.3	82.6	0.197
Fast food	14.5	13.8	0.094
Beverages	13.8	15.1	0.125
Outdoor activities, %			
0–1 h	37	43	0.203
1–2 h	41	42	0.156
>3 h	22	15	0.091
Bedroom time, %			
<12 h	88	84	0.377
>12 h	12	16	0.083
Living environment, %			
Bungalows/building	9/91	8/92	0.433
Urban/rural area	79/21	81/19	0.672
Atopy family history, %	48	52	0.534
Pet raising, %	11	12	0.178
Plush toys, %	28	26	0.139
Parents smoking, %	68	61	0.122
Education background, %			
<master degree	41	46	0.066
>master degree	59	54	0.074
Air conditioning service time, %			
<3 months/year	23	18	0.126
>3 months/year	77	82	0.118
Bedding cleaning, %			
<1 time	17	14	0.139
>1 time	83	86	0.215
Wall material, %			
Wallpaper	13	17	0.190
Organic solvent coating	81	77	0.228
Aqueous coating	6	6	0.316
Floor material, %			
Carpet	11	13	0.265
Ceramic tile	67	75	0.334
Wooden floor	22	12	0.187
Cooking fuel, %			
Coal gas	51	43	0.183
Oil gas	26	31	0.763
Nature gas	23	26	0.683
Duration of disease, %			
<1 year	31	38	0.107
1–2 years	22	20	0.128
>3 years	46	42	0.246
Age of onset	4.2 (3–6)	4.7 (3–6)	0.422
Severity, %			
Mild	22	26	0.371
Moderate	45	46	0.422
Severe	33	28	0.551

Table 5 (continued)

Characteristic	Groups		<i>p</i> value
	AE group	no AE group	
t-IgE	467.8 (185.4–964.1)	298.4 (97.3–713.6)	0.002
IgG4	10.9 (6.2–12.4)	12.8 (10.1–15.6)	0.226
s-IgE of Der f, IU/mL*	46.9 (12.6–75.4)	18.5 (6.6–41.8)	0.001
s-IgE/t-IgE ratios*	26.1 (18.5–41.7)	19.9 (16.1–37.5)	0.086
Blood leukocyte count ($\times 10^9/L$)	5.63 (5.11–7.69)	6.23 (4.98–7.91)	0.377
Blood neutrophil count ($\times 10^9/L$)	3.08 (2.42–3.71)	3.18 (2.53–4.01)	0.426
Blood neutrophil percent, %	48.7 (44.2–58.1)	47.9 (45.1–55.3)	0.164
Blood lymphocyte count ($\times 10^9/L$)	2.02 (1.58–2.89)	2.03 (1.68–2.79)	0.761
Blood lymphocyte percent	34.6 (27.8–41.3)	36.2 (28.1–43.7)	0.644
Blood eosinophil count ($\times 10^9/L$)	0.22 (0.12–0.49)	0.18 (0.13–0.39)	0.029
Blood eosinophil percent, %	5.71 (2.66–8.91)	2.41 (1.55–3.76)	0.017
Blood monocyte count ($\times 10^9/L$)	0.41 (0.32–0.57)	0.43 (0.31–0.58)	0.129
Blood monocyte percent, %	7.42 (6.11–9.54)	7.45 (6.26–8.74)	0.245
Blood basophil count ($\times 10^9/L$)	0.07 (0.02–0.11)	0.06 (0.04–0.11)	0.385
Blood basophil percent, %	1.05 (0.81–1.07)	0.99 (0.85–1.11)	0.195
ECP, ng/mL	38.1 (5.4–119.5)	42.6 (7.9–133.8)	0.266
IL-4, pg/mL	3.7 (2.2–5.6)	3.5 (1.5–4.8)	0.073
IL-5, pg/mL	81.6 (41.2–125.6)	74.5 (40.8–108.4)	0.179
IL-13, pg/mL	1,237.9 (711.8–1,475.9)	1,148.9 (676.3–1,400.3)	0.264
IL-12, pg/mL	79.8 (41.5–123.8)	68.2 (26.7–118.9)	0.073
IFN- γ , pg/mL	213.7 (165.1–326.7)	224.5 (157.2–296.0)	0.146
IL-17, pg/mL	118.3 (81.2–138.9)	126.5 (91.4–174.1)	0.231
IL-10, pg/mL	81.7 (62.5–137.4)	72.6 (60.8–125.8)	0.064
IL-35, pg/mL	133.1 (96.4–178.9)	127.5 (89.8–139.6)	0.172
TGF- β , pg/mL	172.4 (137.8–237.5)	189.8 (111.3–221.5)	0.078

SLIT, sublingual immunotherapy; AEs, adverse events; s-IgE, specific IgE; Der f, dermatophagoides farinae; t-IgE, total IgE; ECP, eosinophil cationic protein. Data are expressed as mean (95% CI). * Geometric mean after logarithmic transformation (95% CI).

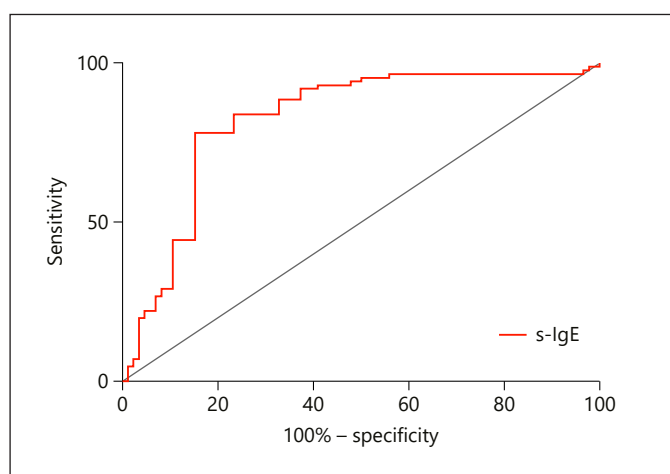


Fig. 1. ROC curves obtained with serum s-IgE levels (decision point, 21.6 IU/mL; sensitivity, 83.7%; specificity, 76.7%) by plotting sensitivity in children with AEs versus 100 – specificity in children without AEs. ROC, receiver operating characteristic; s-IgE, specific IgE; AEs, adverse events.

Table 6. Multivariate logistic analysis of factors associated with safety of SLIT

Markers	OR	95% CI	<i>p</i> value
t-IgE	1.378	0.985–1.964	0.37
s-IgE to Der f	2.784	1.752–2.985	0.01
Blood eosinophil percent	1.358	0.789–2.711	0.03
Blood eosinophil count	1.298	1.113–3.784	0.23

SLIT, sublingual immunotherapy; t-IgE, total IgE; s-IgE, specific IgE; Der f, dermatophagoides farinae; OR, odds ratio; CI, confidence interval.

build-up stage of treatment. The occurrence of severe reaction was very rare. In Cox's review, 2.7 reactions occurred per 1000 SLIT doses and 0.056% was classified as severe [10].

Since the AEs greatly affect the efficacy and compliance of SLIT, we believe that it is very important to con-

firm predictors for AEs. Most previous studies concentrated on allergen extracts or dose-related AEs, only a few studies reported that female, children, or asthmatic patients had a higher risk of reaction [13]. However, no studies investigated the correlation between demographic and laboratory parameters and the occurrence of AEs in children who underwent SLIT yet.

Our results showed that serum s-IgE level was correlated with AEs in multivariate logistic regression analysis. The correlation between s-IgE and AEs had been reported in several studies. Regarding bee venom AIT, an association between high levels of s-IgE to Api m 4 and systemic reactions was reported [14]. In a study on latex immunotherapy, a significant negative correlation was found between the maximal tolerated dose and s-IgE to Hev b 6.01 at baseline [15]. Moreover, s-IgE may help identify children in whom the egg oral immunotherapy is more likely to be safe. Levels above the optimal cutoff (ovomucoid s-IgE 8.85 kU/L) indicated 95% probability of early discontinuation or ongoing reactions over time [16, 17]. A prospective observational study analyzed the risk factors of the systemic reactions in 611 patients who received SIT and found that IgE to olive pollen >20% of t-IgE and IgE to grass pollen >20% of t-IgE were identified as risk factors [18]. Nolte's study found that there was a trend toward an increased incidence of having at least 1 treatment-related AE in subjects who received the grass SLIT tablet with detectable and higher pretreatment Phl p IgE [19]. In the present study, we found that the serum s-IgE levels >21.6 IU/mL had the best sensitivity (83.7%) and specificity (76.7%) for predicting the occurrence of AEs.

Our study had the following limitations: first, selection and recall bias are possible in any observational study like ours. Second, we had no data on some potential confounders, such as the season of treatment. Third, our research was a single-center study which limits our conclusion. Multicenter and large-sample studies are needed to further confirm our results. Fourth, our results are applicable only to children monosensitized to Der f.

Conclusion

The serum s-IgE level was significantly correlated with safety of SLIT in children, which may be helpful for patient selection before SLIT.

Statement of Ethics

The study protocols were approved by local ethics committee boards, and written informed consent was obtained.

Conflict of Interest Statement

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

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Author Contributions

Dr. Wenlong Liu and Renzhong Luo conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Qingxiang Zeng, Yiquan Tang, Shengbao Yan, and Changzhi sun collected the sample, performed the experiment, collected data and statistics, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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