

# Efficacy of Sublingual Immunotherapy in Allergic Rhinitis Children during Coronavirus Disease 2019

Wenlong Liu Qingxiang Zeng Yiquan Tang Shengbao Yan Yan Li  
Shengli Gao Xi Luo Renzhong Luo

Department of Otolaryngology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

## Keywords

Sublingual immunotherapy · Allergic rhinitis · House dust mite · Coronavirus disease 2019 · Total nasal symptoms score

## Abstract

**Background:** Sublingual immunotherapy (SLIT) had good effectiveness for children with allergic rhinitis (AR). However, no studies explored the effect of persistent allergen exposure on SLIT treatment. Coronavirus disease 2019 (COVID-19) restricts outdoor activities of children significantly. We aimed to evaluate the effectiveness of SLIT during this special period. **Methods:** A total of 335 AR children who sensitize to house dust mite (HDM) undergoing SLIT were recruited in this study. The clinical effectiveness and safety were evaluated at different time points using symptom and medication scores. The serum total IgE and specific IgE (sIgE) at different time points were detected by using the Unicap system. **Results:** The total nasal symptoms score (TNSS) and total medication score (TMS) during the epidemic of COVID-19 increased significantly compared with the same period last year ( $p < 0.05$ ), despite that they were still significantly lower than baseline levels ( $p < 0.05$ ). The occurrence of adverse reactions at different time points had no significant differences. We also found that the family of the good response group

had more frequent bedding cleaning. Both the tIgE and sIgE levels had no significant changes during SLIT treatment. **Conclusion:** Our results suggest that continuous HDM exposure reduced the effectiveness of SLIT, whereas effective reduction of HDM levels by frequent bed cleaning will be helpful during the SLIT treatment.

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## Introduction

Allergic rhinitis (AR) is a common global health problem for both adults and children [1]. Patients were affected by combination of symptoms including nasal itching, sneezing, runny nose, and nasal congestion. A recent study suggested that the prevalence of AR was 17.6% for 18 major cities in China [2]. *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1) are 2 of the most important indoor allergens in pediatric and adolescent patients, especially in southern China [3, 4].

The treatment strategies for AR included specific allergen avoidance, pharmacotherapy, and allergy immu-

Wenlong Liu, Qingxiang Zeng, and Yiquan Tang contribute equally to this study.

notherapy (AIT). AIT provides targeted disease-modifying effects in AR and composed of subcutaneous immunotherapy and sublingual immunotherapy (SLIT) [5]. Systematic review had proved the effectiveness of SLIT by improving symptoms of AR and decreasing medication use [6].

Coronavirus disease 2019 (COVID-19) spread rapidly in China from the end of 2019 [7]. The government had adopted strict and effective measures to control the disease. For children, schools were closed, and they had to stay at home from January to at least April. At the same time, most parents were very cautious and outdoor activities of children almost reduced to zero [8]. This situation provided nature intervention to children who underwent SLIT treatment since the exposure to indoor allergens was significantly increased during this period.

A recent position paper or statement suggested the use of SLIT as preferred AIT during COVID since SLIT can be self-administered at home and the adherence to treatment is not affected [9–11]. Therefore, we aimed to evaluate the effectiveness of SLIT during this special period in this study.

## Methods

### Patients

A total of 335 AR children who underwent SLIT were screened. The AR children started SLIT between September 2018 and October 2018, and our observation time ended at April 30, 2020.

The inclusion criteria were as follows: AR was confirmed by typical nasal symptoms longer than 1 year; specific serum IgE level ( $\geq 3.5$  kU/L) against Der p 1, Der f 1, or both (tested allergens included dust mites, pollens, pets, molds, and cockroach); and children had obtained at least a 30% Symptom Medication Score (SMS) reduction compared to their baseline score at the end of study. The main exclusion criteria were as follows: sensitive to other allergens, except for Der p 1 and/or Der f 1; children had poor response to SLIT ( $>30\%$  SMS reduction) at the end of study; and children with asthma diagnosed by a lung function test. All the children had no history of asthma, atopic dermatitis, or other systematic diseases. The study was approved by the Local Ethical Committee (No. 27201), and the written informed consent was provided. The time spent in outdoor activities and bedroom was recorded by telephone survey.

### Immunotherapy

The Der f 1 drops were purchased from Wolwo Pharma Biotechnology Company (Zhejiang, China). The active substance of the drops is saline extract of mite (*Dermatophagoides farinae*) metabolic medium. For safety, the first administration was provided at the clinics, followed by a 30-min observation. The dose escalation stage included 1  $\mu\text{g}/\text{mL}$  drops for the first week, 10  $\mu\text{g}/\text{mL}$  drops for the second week, and 100  $\mu\text{g}/\text{mL}$  drops for the third week, respectively. During the aforementioned stage, 1, 2, 3, 4, 6,

**Table 1.** Baseline information of study subjects undergoing SLIT

Characteristic	
Age, years	8.2 (6–18)
Male/female	113/85
Duration of symptoms, years	1.5 $\pm$ 0.5
Serum sIgE level to Der p1, IU/mL	17.5 (4.3–45.9)
Serum sIgE level to Der f 1, IU/mL	23.6 (3.5–56.1)
Total IgE, IU/mL	188.7 (69.8–637.2)

Der p1, *Dermatophagoides pteronyssinus*; Der f 1, *Dermatophagoides farinae*; SLIT, sublingual immunotherapy; sIgE, specific IgE.

8, and 10 drops of No. 1 to No. 3 drops were provided day after day in 1 week, respectively. At the maintenance stage, 333  $\mu\text{g}/\text{mL}$  drops were given from the fourth week. The drops were administered once a day and roughly at the same time each day. The adverse effects related to SLIT were recorded during the treatment.

### Evaluation of Effectiveness

The nasal symptoms (runny nose, sneezing, blocked nose, and itchy nose) were recorded on a 4-point scale: 0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, and 3 = severe symptoms. The total nasal symptoms score (TNSS) was the sum of each symptom score.

The total medication score (TMS) was recorded according to the recommendations from the World Allergy Organization (WAO) [12]: 1 point for antihistamines, 2 points for nasal corticosteroids, and 4 points for oral corticosteroids. SMS was the sum of TNSS and TMS.

The scores were evaluated before SLIT, 6 months, 1 year after SLIT, and during the COVID-19 pandemic, which was 1.5 years after SLIT. Children who had obtained  $<30\%$ , 30–50%, and  $>50\%$  reduction of SMS during the epidemic of COVID-19 compared to their baseline score were defined as poor, general, and good response groups, respectively.

### Laboratory Parameters

The serum levels of total IgE and specific IgE (sIgE) at different time points were detected by using Phadia CAP (Phadia, Uppsala, Sweden).

### Statistical Analysis

Statistical analyses were performed with SPSS 17.0. The 2-sided  $t$  test was performed for group comparison. The  $\chi^2$  test was used to compare categorical variables. A  $p$  value  $<0.05$  was regarded as statistically significant.

## Results

### Comparison of Effectiveness and Safety at Different Time Points

In a total of 335 AR children, 137 were excluded for different reasons: 98 for poor response, 14 for adverse

**Table 2.** Comparison of effectiveness during SLIT

	Baseline	6 months after SLIT	12 months after SLIT	Epidemic of COVID-19
TNSS	12.16±1.65	4.27±1.29*	4.54±1.41*	6.98±1.33*. #, \$
TMS	1.84±0.69	0.75±0.23*	0.71±0.26*	1.36±0.47*. #, \$
SMS	13.99±2.35	5.13±1.46*	5.78±1.69*	8.39±2.01*. #, \$

All data are presented as medians ± SD. SLIT, sublingual immunotherapy; COVID-19, coronavirus disease 2019; TNSS, total nasal symptoms score; TMS, total medication score; SMS, Symptom Medication Score. \* Compared with baseline group,  $p < 0.05$ . # Compared with 6 months' after SLIT group,  $p < 0.05$ . \$ Compared with 12 months' after SLIT group,  $p < 0.05$ .

event, 10 for failure to adhere to treatment, and 15 for unknown reasons. A total of 198 children were included in the study, and the baseline information is summarized in Table 1.

During the epidemic of COVID-19, 95% children spend <1 h on outdoor activities, whereas 5% children spend 1–2 h on outdoor activities. We also found that 70% children spend more than 12 h in the bedroom, whereas 30% children spend <12 h in the bedroom.

The TNSS, TMS, and SMS during the epidemic of COVID-19 increased significantly compared with 6 months (the same period last year) and 1 year after SLIT treatment. However, the TNSS, TMS, and SMS were still significantly lower than baseline levels (Table 2). The occurrence of adverse reactions between 2 months at the beginning of SLIT treatment and the epidemic of COVID-19 had no significant differences (Table 3).

#### *Comparison of Effectiveness-Related Factors during the Epidemic of COVID-19*

We also divided the children into good response and general response groups according to the TMS. The results showed that the family of the good response group had more frequent bedding cleaning (Table 4).

#### *Comparison of IgE Baseline Levels and the Level under Epidemic of COVID-19*

Both the tIgE and sIgE levels were not changed significantly during the SLIT treatment (Table 5,  $p > 0.05$ ).

## **Discussion**

Previous studies had proved the effectiveness of SLIT in alleviating symptoms of AR and decreasing medication use [6]. However, no studies explored the effect of persistent allergen exposure on the effectiveness of SLIT. CO-

**Table 3.** Comparison of adverse reactions under normal state and the epidemic of COVID-19

	2 months at the beginning of SLIT	Epidemic of COVID-19
Allergic symptom	10	13
Local irritation symptom	7	6
Gastrointestinal symptom	4	7
Other minor symptom	4	5
Systemic symptom	0	0
Total	25	31

SLIT, sublingual immunotherapy; COVID-19, coronavirus disease 2019.

VID-19 in China constricted the outdoor activities of children and increased the indoor allergen exposure significantly, which provides an ideal model for the study of the effect of allergen exposure on effectiveness of SLIT.

Most meta-analyses on SLIT in children have proved their effectiveness in reducing symptoms and medication score, compared with placebo groups in allergic respiratory diseases [12]. In the present study, we found that TNSS and TMS during the epidemic of COVID-19 had a significant decrease compared with the baseline level, proving the effectiveness of SLIT, which was in agreement with other studies [13, 14]. However, the TNSS and TMS during the epidemic of COVID-19 increased significantly compared with 6 months (the same period last year) and 1 year after SLIT treatment, suggesting that increased allergen exposure reduced the effectiveness of SLIT. We also found that the occurrence of adverse reactions between the first month of SLIT treatment, which is the time children had the most adverse reactions, and the epidemic of COVID-19 had no significant differences.

A multi-center study confirmed that southern cities in China, such as Guangzhou, have up to 50 times more

**Table 4.** Comparison of effectiveness related factors during the epidemic of COVID-19

Characteristic	Group		p value
	good response	general response	
n	125	73	0.123
Age, years	8.3 (6.1–17)	8.5 (6.4–16.1)	0.245
Male, n (%)	71 (57)	39 (54)	0.356
Living environment, %			
Bungalows/building	7/93	8/92	0.098
Urban/rural area	81/19	75/25	0.133
Parents smoking, %	52	61	0.276
Bedding cleaning, %			
<1 time/week	22	47	<b>0.003</b>
>1 time/week	78	53	<b>0.001</b>
Floor material, %			
Carpet	17	29	0.054
Ceramic tile	68	52	0.138
Wood floor	15	19	0.296

COVID-19, coronavirus disease 2019.

**Table 5.** Comparison of total and sIgE levels at different time points

	Baseline	12 months after SLIT	Epidemic of COVID-19
Serum sIgE level to Der p1, IU/mL	17.5 (4.3–45.9)	13.4 (5.7–56.3)	21.6 (4.9–41.8)
Serum sIgE level to Der f 1, IU/mL	23.6 (3.5–56.1)	29.7 (4.8–72.5)	18.4 (5.5–44.6)
Total IgE, IU/mL	188.7 (69.8–637.2)	145.3 (51.6–412.7)	171.3 (82.6–519.8)

Der p1, *Dermatophagoides pteronyssinus*; Der f 1, *Dermatophagoides farinae*; SLIT, sublingual immunotherapy; COVID-19, coronavirus disease 2019; sIgE, specific IgE.

house dust mite (HDM) major allergens than northern and western cities of China, which was consistent with an HDM SPT sensitization prevalence from almost 80% in the southern parts to about 40% in northern China [15]. The features of Guangzhou's weather, such as high temperature and high humidity, provided optimal conditions for HDM propagation [16]. Moreover, long duration in environments with poor ventilation increases the chance of exposure to HDMs. Consistently, we found that parents in the good response group had more frequent bed cleaning than those in the general response group. The results are reasonable since more frequent bed cleaning reduced HDM levels. Moreover, our data suggested that children spend more time in the bedroom during the epidemic of COVID-19 than normal condition, which may be contribute to longer night sleep and afternoon nap [17]. Therefore, frequent bed cleaning may play more important role during this special period.

The sIgE plays important roles in AR. Previous studies observed that sIgE increases in the early period of SLIT

and then decreases [18, 19]. Another study suggested that sIgE was not strongly associated with the reported symptoms [20]. Our results suggested that tIgE and sIgE levels during the epidemic of COVID-19 had no significant difference compared with the levels 1 year after SLIT. Moreover, sIgE have seasonal variations. Taken together, these results suggested that sIgE was not an optimal indicator to evaluate the effectiveness of SLIT.

Our study had following limitations. First, the concentration of HDM at different time points was not measured since this is a retrospective study. However, we believe that the levels of HDM at the same season were stable in Guangzhou. Second, our research was a one-center study, which limits our conclusion. Multicenter and large sample studies were needed to further confirm our results. Third, external anxiety may be a potential confounder during a home quarantine, especially for adverse events. Therefore, our data were obtained immediately post-pandemic when the quarantine was lifted to reduce the psychosocial aspect to the findings. A previous study had

found that 18.9% of students reported anxiety symptoms during this period [21]. However, some findings suggested that children in the nonsevere area did not suffer major psychological distress during the outbreak [22]. Therefore, the exact effect of anxiety on the treatment of SLIT needed further exploration. Most of our study subjects were 6–10 years old (70%), which was an age that may experience anxiety to a less degree. So the conclusion of our study may not be affected. In summary, our results suggested that continuous HDM exposure reduced the effectiveness of SLIT, whereas effective reduction of HDM levels by frequent bedding cleaning will be helpful during the SLIT treatment.

### Statement of Ethics

The study was approved by the Guangzhou Women and Children's Medical Center's Ethical Committee (No. 27201), and the written informed consent was provided by parents.

### 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 Yan Li conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Yiquan Tang, Shengbao Yan, Shengli Gao, Xi Luo, and Renzhong Luo coordinated and supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted.

### Data Availability Statement

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



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