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

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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 sensitized 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.

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 immunotherapy.
Sublingual Immunotherapy in Allergic Rhinitis Children

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 (≥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 the 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 systemic 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) metabolized medium. For safety, the first administration was provided at the clinics, followed by a 30-min observation. The dose escalation stage included 1 μg/mL drops for the first week, 10 μg/mL drops for the second week, and 100 μg/mL drops for the third week, respectively. During the aforementioned stage, 1, 2, 3, 4, 6, 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 μg/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 χ² test was used to compare categorical variables. A p value <0.05 was regarded as statistically significant.

Table 1. Baseline information of study subjects undergoing SLIT

| Characteristic          | Value                  |
|-------------------------|------------------------|
| Age, years              | 8.2 (6–18)             |
| Male/female             | 113/85                 |
| Duration of symptoms, years | 1.5±0.5               |
| Serum sIgE level to Der p1, IU/mL | 17.5 (4.3–45.9)       |
| Serum sIgE level to Der f1, IU/mL | 23.6 (3.5–56.1)       |
| Total IgE, IU/mL        | 188.7 (69.8–637.2)     |

Der p1, Dermatophagoides pteronyssinus; Der f1, Dermatophagoides farinae; SLIT, sublingual immunotherapy; sIgE, specific IgE.

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

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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. COVID-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 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.

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

| Allergic symptom | 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                    |
| Symptom Medication Score | 0                               | 0                    |
| Total            | 25                               | 31                   |

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

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**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      | 0.003  |
| >1 time/week                                | 78             | 53      | 0.001  |
| 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 f1, 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 f1, *Dermatophagoides farinae*; SLIT, sublingual immunotherapy; COVID-19, coronavirus disease 2019; sIgE, specific IgE.
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.

**References**

1. Mims JW. Epidemiology of allergic rhinitis. Int Forum Allergy Rhinol. 2014;4 Suppl 2: S18–20.
2. Wang XD, Zheng M, Lou HF, Wang CS, Zhang Y, Bo MY, et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. Allergy. 2016;71:1170–80.
3. Rod NH, Kristensen TS, Lange P, Prescott E, Diderichsen F. Perceived stress and risk of adult-onset asthma and other atopic disorders: a longitudinal cohort study. Allergy. 2012;67:1408–14.
4. Andiappan AK, Puan KJ, Lee B, Nardin A, Poidinger M, Connolly J, et al. Allergic airway diseases in a tropical urban environment are driven by dominant mono-specific sensitization against house dust mites. Allergy. 2014; 69:501–9.
5. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma and Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol. 2013;131:1288–96.e3.
6. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA. 2013; 309:1278–88.
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13.
8. Moore SA, Faulkner G, Rhodes RE, Brussoni M, Chulak-Bozzer T, Ferguson LJ, et al. Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: a national survey. Int J Behav Nutr Phys Act. 2020;17:85.
9. Pfarr O, Klimek I, Jutel M, Akdis CA, Bousquet J, Breiteneder H, et al. COVID-19 pandemic: practical considerations on the organization of an allergy clinic–an EAACI/ARIA position paper. Allergy. 2020;76:684–76.
10. Malipiero G, Paoletti G, Puggioni F, Racca F, Ferri S, Marsala A, et al. An academic allergy unit during COVID-19 pandemic in Italy. J Allergy Clin Immunol. 2020;146:227.
11. Oliver P, Klimek I, Jutel M, Akdis C, Bousquet J, Akdis M, et al. Handling of allergen immunotherapy in the COVID-19 pandemic: an ARIA-ARACI statement. Allergy. 2020;75:1546–54.
12. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blais M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014;7:6.
13. Masuyama K, Okamoto Y, Okamiya K, Azuma R, Fujinami T, Riis B, et al. Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet in Japanese children. Allergy. 2018;73:2352–363.
14. Guo Y, Li Y, Wang D, Liu Q, Liu Z, Hu L. A randomized, double-blind, placebo controlled trial of sublingual immunotherapy with house-dust mite extract for allergic rhinitis. Am J Rhinol Allergy. 2017;31:42–7.
15. Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G, et al. Chinese Alliance of Research on Respiratory Allergic Disease (CAARD): a multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. Allergy. 2009;64(7):1083–92.
16. Andiappan AK, Puan KJ, Lee B, Nardin A, Poidinger M, Connolly J, et al. Allergic airway diseases in a tropical urban environment are driven by dominant mono-specific sensitization against house dust mites. Allergy. 2014; 69:501–9.

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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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17 Liu W, Zeng Q, Luo R. Predictors for short-term efficacy of allergen-specific sublingual immunotherapy in children with allergic rhinitis. _Meditators Inflamm._ 2020; 2020: 1847061.

18 Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. _J Allergy Clin Immunol._ 2014; 133: 621–31.

19 Rondon C, Campo P, Salas M, Aranda A, Molina A, Gonzalez M, et al. Efficacy and safety of _D. pteronyssinus_ immunotherapy in local allergic rhinitis: a double-blind placebo-controlled clinical trial. _Allergy._ 2016; 71: 1057–61.

20 Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005–2006. _J Allergy Clin Immunol._ 2011; 127: 1226–35.

21 Xie X, Xue Q, Zhou Y, Zhu K, Liu Q, Zhang J, et al. Mental health status among children in home confinement during the coronavirus disease 2019 outbreak in Hubei Province, China. _JAMA Pediatr._ 2020; 174: 898–900.

22 Yue J, Zang X, Le Y, An Y. Anxiety, depression and PTSD among children and their parent during 2019 novel coronavirus disease (COVID-19) outbreak in China. _Curr Psychol._ 2020; 14: 1–8.