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ORIGINAL ARTICLE

Efficacy and safety of sublingual immunotherapy with *Dermatophagoides farinae* drops in pre-school and school-age children with allergic rhinitis



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KEYWORDS

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Abstract

Background: The safety and efficacy of sublingual immunotherapy (SLIT) have been confirmed by many studies. However, in China, the research on efficacy and safety in young and older children with allergic rhinitis (AR) is still rare.

Objective: The aim of this retrospective study is to evaluate the efficacy and safety of SLIT with *Dermatophagoides farinae* drops in pre-school and school-age children with AR.

Methods: A total of 282 subjects aged 2–13 years with AR received a two-year course of sublingual immunotherapy along with pharmacotherapy. According to the age, patients were defined as the pre-school group (2–6 years old, $n = 116$) and school-age group (7–13 years old, $n = 166$). Total nasal rhinitis symptom scores (TNSS), visual analogue score (VAS) and total medication scores (TMS) were evaluated at four time points: baseline, after SLIT for half a year, one year and two years. The adverse events (AEs) were evaluated at each visit.

Results: After two-year SLIT, the four rhinitis symptom scores, TNSS, VAS and TMS scores were significantly lower than baseline (all $P < 0.05$). The comparison of efficacy between one and two-year duration showed no significant difference in global clinical outcomes (all $P > 0.05$). In addition, there were no significant differences between the pre-school and school-age group in TNSS (all $P > 0.05$), VAS (all $P > 0.05$) and TMS scores ($P > 0.05$) after SLIT for half a year, one year and two years. No severe systemic AEs were reported.

Conclusion: SLIT with *D. farinae* drops is clinically effective and safe in pre-school and school-age patients with house dust mites (HDMs)-induced AR.

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Introduction

Allergic rhinitis (AR) is characterised by excessive eosinophil infiltration, Th2 cytokine responses, elevated levels of allergen-specific IgE, mucus secretion and airway hyperresponsiveness.¹ In China, the prevalence of AR in children has increased from 9.1% in 2001² to 15.4% in 2010,³ and house-dust mites (HDMs) have been documented to be the most prevalent allergens.⁴ Symptomatic treatment is based on antihistamines and corticosteroids. Apart from eliminating allergens, which can be difficult, allergen specific immunotherapy (ASIT) is at present the only aetiological treatment able to alter disease progression.^{5,6}

The latest position paper document ASIT has practically no controversy in the treatment of AR and allergic asthma.⁷ And in the latest national guidelines for the diagnosis and treatment of AR, it is suggested that ASIT should be used as first-line treatment for AR.⁸ As a new route of administration of ASIT, the safety and efficacy of sublingual immunotherapy (SLIT) have been confirmed by meta-analysis and systematic review.^{9–11} However, in China, the research on efficacy and safety of SLIT in young children and older children is still rare.

Materials and methods

Subjects

In total, 282 patients aged 2–13 years were involved from December 2012 to March 2014. The inclusion criteria were: (1) diagnosed with moderate-to-severe/persistent AR; (2) allergic symptoms and signs such as runny nose, itchy nose, sneezing, nasal crease, pale and swollen nasal mucosa, and watery discharge; (3) positive clinical history of HDM allergy and positive skin-prick test (SPT) for *D. farinae* and serum-specific immunoglobulin E (IgE) ≥ 0.7 KU/L. The exclusion criteria included: (1) patients with immunodeficiency; (2) with bronchial asthma, acute respiratory infections and other diseases that may cause respiratory symptoms; and (3) patients having received allergen-specific immunotherapy previously.

The study was approved by the ethics committee of the Beijing Children's Hospital, Capital Medical University. We obtained informed consent from all the patients.

SLIT with HDM extract

All patients were treated with sublingual immunotherapy by *Der. f* extracts (CHANLLERGEN, Zhejiang Wolwo

Bio-Pharmaceutical Co., Ltd., Huzhou, Zhejiang, China) in this study, which were officially approved by the Chinese Food and Drug Administration in 2006. The biologically standardised extracts were labelled in concentration of total protein and used in the form of drops (No. 1 1 μ g/mL; No. 2 10 μ g/mL; No. 3 100 μ g/mL and No. 4 333 μ g/mL). Subjects were instructed to take increasing dose from No. 1 to No. 3 during the first three weeks. 1, 2, 3, 4, 6, 8, 10 drops were given day after day in a week, respectively. Children under 14 years old took three drops of No. 4 solution daily in the maintenance therapy phase from the fourth week. The first dose taken was required to be performed under medical supervision. Subjects were instructed to self-administer at home daily and keep the drops under the tongue for 1–3 min, then swallow and not to drink for 15 min. Guardians of the young children were asked to help administer the doses. In case of adverse events, the dosage increase was properly delayed or reduced under the guidance of physicians.

Symptoms, medication scoring system and visual analogue scale

Before the treatment, nasal symptoms (nasal discharge, nasal obstruction, itching, sneezing), medication use and overall severity of symptoms of patients were recorded as baseline values in files. During the treatment, patients were asked to accept follow-up visit in hospital or by telephone every six months. The total nasal symptoms score (TNSS), total medication score (TMS) and visual analogue score (VAS) of subjects were evaluated by physicians at each visit. TNSS was the sum of four nasal symptoms scores. These nasal symptoms were evaluated according to a 0–3 point scoring system¹² (Table 1). TMS was evaluated as 0–3 points according to the medicine use⁸ (Table 2). VAS represents the overall severity of symptoms through a 10-cm visual analogue scale.¹³ A 10-point scoring system was used for assessing subjective symptoms. 0 points indicated ‘no symptom’, 10 points indicated ‘extremely severe symptom’.

Adverse events (AEs)

All of the AEs reported during the study period were recorded on a diary card, as were aggravating local reactions/moderate reactions, drug therapy or other treatments as needs and/or proper delay or reducing of SLIT dose. AEs were rated on five levels (0–4 scale) according to the grading system proposed by the European Academy of Allergy and

Table 1 Nasal symptom scores.

Score	Sneeze ^a	Rhinorrhoea ^b	Nasal obstruction	Itching
1	3–5	≤ 4	Congestion but no mouth breathing	Intermittent itching
2	6–10	5–9	Severe congestion with occasional mouth breathing	Tolerable itching
3	≥ 11	≥ 10	Severe congestion with occasional mouth breathing during the whole day	Intolerable itching

^a Consecutive number.

^b The daily count of blowing your nose.

Table 2 Medication scores.

Score	Anti-allergic drug
1	Oral and/or topical antihistamine Anti-leukotrienes Bronchodilator drugs, β_2 -agonists bronchodilator drugs
2	Nasal corticosteroids/inhaled corticosteroids
3	Oral corticosteroids Combination therapy (corticosteroids and β_2 -agonists)

Clinical Immunology,¹⁴ which is based on the rate of onset and severity of the reactions.

Statistical analysis

The statistical analysis was performed with SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA). The statistical significance of difference was determined by the non-parametric Mann–Whitney *U* test or Wilcoxon signed rank test. $P < 0.05$ (*) represented significant difference.

Table 3 Baseline characteristics and demography.

Character	Patients
Number of subjects	282
Age (years), mean \pm SD	7.32 \pm 2.56
Male sex (%)	69.15 ($n = 195$)
Female sex (%)	30.85 ($n = 87$)
Years with AR	2.51 \pm 1.86

Results

Population characteristics

A total of 282 subjects aged 2–13 years old were involved in this study. Baseline characteristics of 282 subjects were reported before treatment. Age, sex ratio and course of disease were recorded and are shown in Table 3.

Effects on rhinitis symptom scores, TMS and VAS

After two-year SLIT, the four rhinitis symptom scores, TNSS, VAS and TMS scores were significantly lower than baseline (Sneezing: $Z = 16.243$; Rhinorrhoea: $Z = 16.488$; Nasal

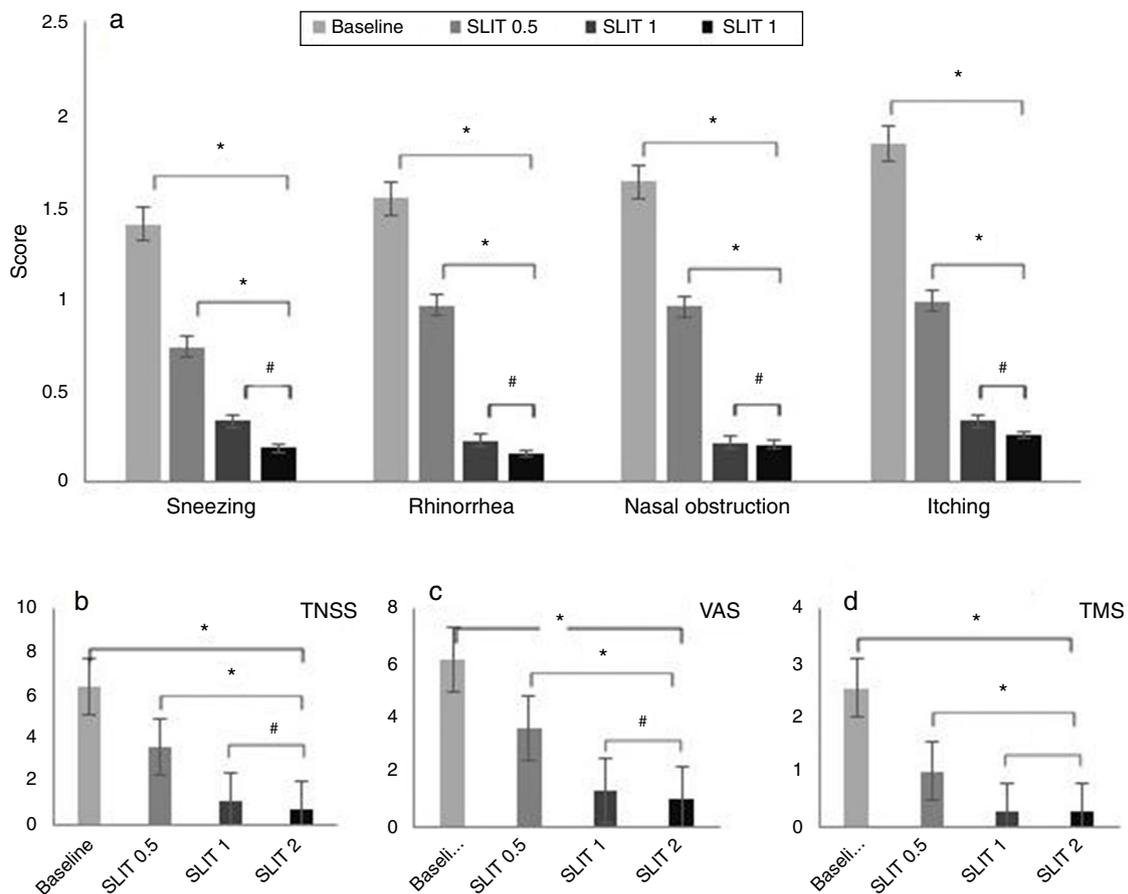


Figure 1 Four rhinitis symptom scores, TNSS, VAS and TMS scores before and after SLIT treatment. (a) Four rhinitis symptom scores, (b) TNSS, (c) VAS, and (d) TMS. There was a significant decline in four rhinitis symptom scores, TNSS, VAS and TMS scores after treatment (* $P < 0.05$, # $P > 0.05$, compared with the baseline value). SLIT = sublingual immunotherapy; TNSS = total nasal symptom score; VAS = visual analogue scale; TMS = total medication score.

obstruction: $Z = 17.450$; Itching: $Z = 17.138$; TNSS: $Z = 21.657$; VAS: $Z = 21.690$; TMS: $Z = 20.108$, all $P < 0.05$).

After two-year SLIT, compared with half one year duration, all scores in patients were significantly decreased (Sneezing: $Z = 6.996$; Rhinorrhoea: $Z = 9.752$; Nasal obstruction: $Z = 9.426$; Itching: $Z = 9.459$; TNSS: $Z = 13.373$; VAS: $Z = 12.231$; TMS: $Z = 8.382$, all $P < 0.05$).

The comparison of efficacy between one and two-year duration showed no significant difference in global clinical outcomes (Sneezing: $Z = 2.202$; Rhinorrhoea: $Z = 1.027$; Nasal obstruction: $Z = 0.130$; Itching: $Z = 0.719$; TNSS: $Z = 2.022$; VAS: $Z = 2.348$; TMS: $Z = 0.147$, all $P > 0.05$) (Fig. 1a–d).

Efficacy and safety in pre-school and school-age children

In addition, there were no significant differences between the pre-school group and school-age group in TNSS (Baseline: $Z = 0.053$; SLIT 0.5: $Z = 0.010$; SLIT 1: $Z = 2.132$; SLIT 2: $Z = 0.020$, all $P > 0.05$), VAS (Baseline: $Z = 0.689$; SLIT 0.5: $Z = 2.555$; SLIT 1: $Z = 0.209$; SLIT 2: $Z = 0.001$, all $P > 0.05$) and TMS scores (Baseline: $Z = 0.522$; SLIT 1: $Z = 1.468$; SLIT 2: $Z = 0.267$, all $P > 0.05$) after SLIT for half a year, one year and two years (Fig. 2a–c).

None of the children required hospitalisation or withdrew from the study because of AEs. No severe systemic AEs, anaphylaxis, or use of adrenaline were reported. 30 patients reported 36 AEs. Sixteen and 20 AEs were found in the pre-school group and school-age group, respectively. The majority of AEs were slight local reactions and all AEs were

relieved. There were no significant differences between the pre-school group and school-age group ($\chi^2 = 0.063$, $P > 0.05$) (Fig. 2d).

Discussion

In a randomised double-blind placebo controlled study, Bahceciler et al.¹⁵ found that half-a-year SLIT can obviously improve the lung function of AR with allergic asthma (AS) in children, and reduce inhaled corticosteroids. A study of 3–13 year old children with AR for one year of SLIT, found that after treatment for seven months, compared with the control group, SLIT group has sustained efficacy during the treatment period.¹⁶ A large number of research data showed that SLIT can significantly reduce the severity of symptoms in AR. The effect is closely related to the course of SLIT, but related research is still rare. In this study, we found that the subjective symptoms decreased significantly after SLIT for six months. In addition, there are no significant differences between the one- and two-year SLIT groups. The efficacy has sustained during the whole SLIT period, and the symptoms gradually stabilised after one year.

Dust mite is one of the most common indoor allergens and the main cause of AR in children. In daily life, especially for children, it is very difficult to avoid exposure to dust mites, so the early intervention of AR caused by dust mites should be paid enough attention.¹⁷ Shao et al.¹⁶ found that SLIT with *D. farinae* extracts is effective in subjective and objective symptom improvements in children aged 3–5 years. But in China, there are few reports about SLIT in

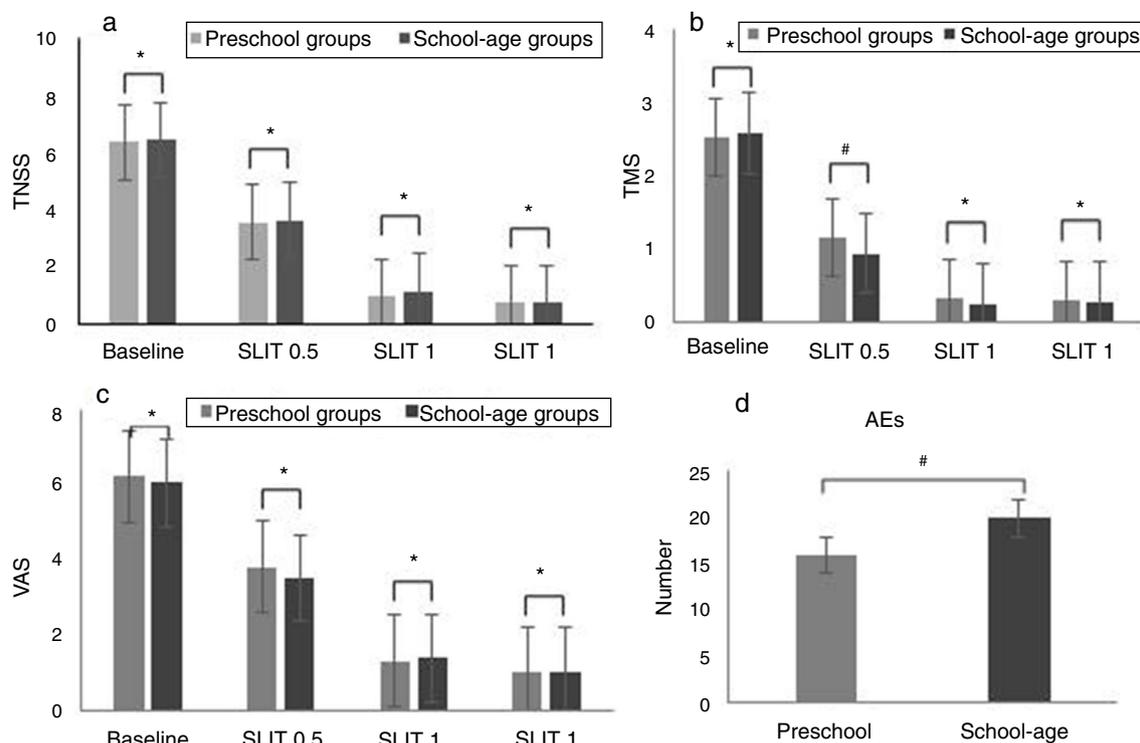


Figure 2 TNSS, VAS and TMS scores in pre-school and school-age groups before and after SLIT treatment. (a) TNSS, (b) TMS, (c) VAS (* $P < 0.05$, # $P > 0.05$, compared between two subgroups). SLIT = sublingual immunotherapy; TNSS = total nasal symptom score; VAS = visual analogue scale; TMS = total medication score; AEs = adverse events.

children with AR, especially in young children. In this study, 282 children with dust mite AR were divided into pre-school (2–6 years old) and school-age (7–13 years old) groups, and the results showed that there were no significant differences in TNSS, VAS and TMS scores between these two groups after SLIT for half a year, one year and two years. It is worth mentioning that 15 children aged 2–3 years were included in our study, and the symptoms have been greatly improved after two-year SLIT.

During the course of treatment, 30 patients reported 36 adverse reactions, the total incidence of adverse reactions was only 10%. Moreover, the majority of AEs were slight local reactions. These AEs generally occurred during the first few weeks of treatment and were relieved within a few days without any medical intervention. Other AEs were relieved after dose adjustment of *D. farinae* extracts along with medication (oral antihistamines or intranasal corticosteroid) according to the suggestions from physician.

Conclusion

SLIT with *D. farinae* drops is clinically effective and safe in pre-school and school-age patients with HDM-induced AR, including very young children less than four years old.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

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References

- Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378:2112–22.
- Wong GW, Hui DS, Chan HH, Fok TF, Leung R, Zhong NS, et al. Prevalence of respiratory and atopic disorders in Chinese school children. *Clin Exp Allergy*. 2001;31:1225–31.
- Zhao J, Bai J, Shen K, Xiang L, Huang S, Chen A, et al. Self-reported prevalence of childhood allergic diseases in three cities of China: a multicenter study. *BMC Public Health*. 2010;10:551.
- Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. *Allergy*. 2009;64:1083–92.
- Petalas K, Durham SR. Allergen immunotherapy for allergic rhinitis. *Rhinology*. 2013;51:99–110.
- Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy*. 2005;60:4–12.
- Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556–68.
- Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery. Chinese Medical Association. Chinese guidelines for diagnosis and treatment of allergic rhinitis. *Chin J Otorhinolaryngol Head Neck Surg*. 2016;51:6–24.
- Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol*. 2009;124:157–61.
- Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol*. 2009;102:22–8.
- Röder E, Berger MY, De Groot H, Van Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol*. 2008;19:197–207.
- Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy*. 2014;69:854–67.
- Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy*. 2007;62:367–72.
- Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E, et al. Standards for practical allergen-specific immunotherapy. *Allergy*. 2006;61:1–20.
- Bahceciler NN, Isik U, Barlan IB, Başaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double blind, placebo-controlled study. *Pediatr Pulmonol*. 2001;32:49–55.
- Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, et al. Efficacy and safety of sublingual immunotherapy in children aged 3–13 years with allergic rhinitis. *Am J Rhinol Allergy*. 2014;28:131–9.
- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy*. 2008;63:8–160.