

Efficacy and safety of house dust mite sublingual immunotherapy in monosensitized and polysensitized children with respiratory allergic diseases

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Background: The efficacy of single-allergen-specific immunotherapy in polysensitized subjects is a matter of debate. This study aimed to investigate the efficacy of house dust mite (HDM) sublingual immunotherapy (SLIT) in monosensitized and polysensitized children.

Methods: A total of 112 children, aged 4 to 13 years old, with HDM-induced respiratory allergic diseases were allocated to a monosensitized group (n = 56) or a polysensitized group (n = 56). Both groups were treated by standard pharmacotherapy and SLIT with *Dermatophagoides farinae* (American HDM) extracts for 52 weeks. Symptoms, medications, visual analogue scale (VAS), and presence of adverse events (AEs) were assessed once a month. Skin-prick test (SPT) was done before and after treatment. After treatment, subjects in the polysensitized group who completed the study were further analyzed as subgroup 1 (n = 20) and subgroup 2 (n = 15) according to the number of co-existing allergens.

Results: Forty-one subjects in the monosensitized group and 35 subjects in the polysensitized group completed the study. The global clinical parameters had significantly improved after treatment, with no significant difference between the monosensitized and polysensitized group

throughout this period (all $p > 0.05$). The comparison among the monosensitized group, subgroup 1, and subgroup 2 indicated that there was no significant difference in symptoms scores and VAS at each scheduled follow-up visit. There was also no significant difference in total medications score (TMS) in the monosensitized group, subgroup 1, and subgroup 2 after week 24 (all $p > 0.05$). No severe systemic AEs were reported.

Conclusion: No significant difference was observed in the clinical effects of HDM SLIT between polysensitized and monosensitized children with respiratory allergic diseases.

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Key Words:

Allergy; efficacy; monosensitized; polysensitized; sublingual immunotherapy

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Polysensitization is an immunologic phenomenon that is clinically significant and relevant from an epidemiological point of view, as reported in a recent survey.¹ In Europe and the United States, 51% to 81% of allergic subjects are

polysensitized,^{2,3} and this proportion is about 60.2% in China.⁴ Particularly, house dust mite (HDM) allergen has been documented to be the most prevalent allergen of the polysensitized subjects in China, rather than pollens, which are known as the major inhaled allergens in European polysensitized subjects.^{1,4,5} The polysensitization has caused difficulties for the allergist in prescribing allergen-specific immunotherapy. Most of the immunotherapy formulations in Europe are single-allergen extracts, based on the viewpoint that polysensitization does not necessarily lead a patient to be clinically polyallergic; however, physicians in the United States tend to provide preparations containing an average of 8 different allergen components.⁴ Recent clinical trials have indicated that single-allergen immunotherapy with grass pollen extracts was safe and effective in

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polysensitized subjects.^{2,6-8} Single-allergen immunotherapy with HDM extracts was also proved to be effective in allergic children.⁹ However, there is a continuing debate concerning the efficacy of single-allergen sublingual immunotherapy (SLIT) in polysensitized subjects, which requires further delineation considering that the majority of allergic subjects are sensitized to more than 1 allergen.⁸ Therefore, this study was designed to compare the efficacy of standardized HDM SLIT between monosensitized and polysensitized children and investigate the potential relationship between the efficacy and sensitization status.

Patients and methods

This was a prospective, randomized study that followed patients with respiratory allergic diseases from January 2009 to October 2010 to evaluate treatment efficacy.

A total of 112 children (4–13 years old) in Nanjing, China, who suffered from allergic rhinitis with controlled asthma according to Allergic Rhinitis and its Impact on Asthma Guidelines (ARIA) or Global Initiative for Asthma (GINA) were recruited for this study during a 6-month run-in period.^{10,11} The mandatory inclusion criteria were as follows: (1) diagnosed with moderate-to-severe or persistent allergic rhinitis without severe asthma; (2) having a clinical history of mite allergy and sensitization to *Dermatophagoides farinae* (*D.f.*) and/or *Dermatophagoides pteronyssinus* (*D.p.*) as confirmed by a positive skin-prick test (SPT) with a wheal size of ≥ 3 mm in diameter and grade ≥ 2 in area; and (3) a forced expiratory volume in 1 second (FEV_1) $\geq 70\%$ of predicted volume. Exclusion criteria were as follows: (1) patients suffering from other concomitant immune system diseases; or (2) patients having received allergen-specific immunotherapy previously.

SPT including 13 restrictive aeroallergens (*D.f.*, *D.p.*, *Blomia tropicalis*, dog [*Canis familiaris*], cat [*Felis domesticus*], *Periplaneta americana*, *Blattella germanica*, *Artemisia vulgaris*, *Ambrosia artemisifolia*, mixed grasses, mixed trees, mould mix I and mould mix IV; ALK-AbelloÂ, Hùrsholm, Denmark) was performed according to standard protocol before and after treatment, using histamine (positive control) and normal saline (negative control) for comparison. A wheal size of ≥ 3 mm was deemed as positive. The wheal area of allergens was graded based on the ratio (%) of wheal area between allergen and positive control as follows: grade 1 = 1% to 49%; grade 2 = 50% to 99%; grade 3 = 100% to 199%; and grade 4 = $\geq 200\%$. The skin reaction to *D.f.* and/or *D.p.* was evaluated before and after treatment.

This preliminary study was approved by the Ethics Committees of Nanjing Children's Hospital Affiliated to Nanjing Medical University, and performed in compliance with the ethical guidelines. Guardians of each child had fully understood and signed the patient informed consent form. According to SPT results, children only sensitive to *D.f.* and/or *D.p.* were allocated into the monosensitized group ($n = 56$), and the children who were sensitized to *D.f.*

and/or *D.p.* and other coexisting inhaled allergens were enrolled into the polysensitized group ($n = 56$). All of the 112 children had received SLIT with standardized *D.f.* extracts (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Deqing, Zhejiang Province, China) for 1 year, and medications were permitted according to ARIA and GINA throughout the study.^{10,11} At the end of study, subjects in the polysensitized group who completed the study had been further analyzed in 2 subgroups: subgroup 1 (subject sensitive to *D.f.* and/or *D.p.* with 1 other coexisting allergen; $n = 20$) and subgroup 2 (subject sensitive to *D.f.* and/or *D.p.* with 2 or more other coexisting allergens; $n = 15$), to investigate the potential relationship between efficacy and sensitization status.

The biologically standardized *D.f.* extracts were used in the form of drops (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd.) and were labeled by concentration of total protein (No. 1, 1 $\mu\text{g/mL}$; No. 2, 10 $\mu\text{g/mL}$; No. 3, 100 $\mu\text{g/mL}$; No. 4, 333 $\mu\text{g/mL}$; and No. 5, 1000 $\mu\text{g/mL}$), which were determined by bicinchoninic acid (BCA) protein assay, and the biological activity of allergen extracts was detected by a method of preparing standard serum mixture.¹² All subjects were asked to take daily increasing doses (from No. 1 to No. 3) according to the manufacturer's instructions during the 3-week up-dosing phase. Subjects younger than 14 years old were instructed to take 3 drops of the No. 4 solution once daily as the maintenance dosage after week 4. 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 to 3 minutes, then swallow and not to drink for 15 minutes. 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.

Subjects were required to visit the hospital at weeks 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, and 52, and record all symptoms, medication consumption, and visual analogue scale (VAS) score during the study period. Each nasal symptom (sneezing, nasal discharge, itching, and nasal obstruction) was evaluated according to a scoring system from 0 to 3 points, as follows: (1) sneezing (successive numbers per time): none = 0 points; 3 to 5 = 1 point; 6 to 10 = 2 points; and $\geq 11 = 3$ points; (2) nasal discharge (times per day): none = 0 points; $\leq 5 = 1$ point; 5 to 9 = 2 points; and $\geq 10 = 3$ points; (3) itching: none = 0 point; intermittent itching = 1 point; tolerable itching = 2 points; and intolerable itching = 3 points; (4) nasal obstruction: none = 0 points; congestion but no mouth breathing = 1 point; severe congestion with occasional mouth breathing = 2 points; severe congestion with mouth breathing during the whole day = 3 points. The total nasal symptoms score (TNSS) was the sum of 4 nasal symptoms scores. Asthmatic symptoms in children with asthma were also recorded. The daytime asthma symptoms were scored from 0 to 5 points according to the general severity of wheeze, shortness of breath, dyspnea, and cough and its impact on daily life. The nocturnal symptoms were scored from 0 to 4 points according to

TABLE 1. Demographic and clinical characteristics

		Polysensitized (n = 56)		
	Monosensitized (n = 56)	Total (n = 56)	Subgroup 1 (n = 20)	Subgroup 2 (n = 15)
Gender ratio (male:female)	2.73:1	2.18:1	2.33:1	2:1
Age, years (mean $\pm$ SD)	6.80 $\pm$ 2.77	7.06 $\pm$ 2.22	6.80 $\pm$ 2.04	7.40 $\pm$ 2.47
Positive allergens (n)	1	2.71 $\pm$ 1.05	2	3.67 $\pm$ 0.98
Clinical data score (mean $\pm$ SD)				
TASS	1.32 $\pm$ 1.08	1.43 $\pm$ 1.56	1.12 $\pm$ 1.23	1.80 $\pm$ 1.90
TNSS	4.85 $\pm$ 2.08	4.31 $\pm$ 2.63	4.15 $\pm$ 2.64	4.53 $\pm$ 2.70
TMS	2.01 $\pm$ 1.18	2.36 $\pm$ 1.51	1.55 $\pm$ 1.05	3.43 $\pm$ 1.36 ^{a,b}
VAS	2.78 $\pm$ 1.52	3.47 $\pm$ 1.78	3.47 $\pm$ 1.35	3.48 $\pm$ 2.27
Grade of skin reaction ^c	3.52 $\pm$ 0.52	3.61 $\pm$ 0.42	3.65 $\pm$ 0.40	3.57 $\pm$ 0.46

^aCompared with the monosensitized group.

^bCompared with subgroup 1.

^cSkin reaction to *D.f.* or *D.p.* or average of skin reaction to *D.f.* and *D.p.*

D.f. = *Dermatophagoides farinae*; *D.p.* = *Dermatophagoides pteronyssinus*; SD = standard deviation; TASS = total asthma symptoms score; TMS = total medication score; TNSS = total nasal symptoms score; VAS = visual analogue score.

the frequency of nocturnal and early morning awakening by asthma.¹³ The total asthma symptoms score (TASS) was the sum of daytime and nocturnal asthma symptoms scores. The TNSS and TASS were evaluated monthly.

The following medications were allowed: oral antihistamine, oral or topical corticosteroid, antileukotrienes, and β_2 -agonists. The total medications score (TMS) was evaluated as follows (per day): 1 = antihistamine or antileukotrienes or β_2 -agonists; 2 = topical corticosteroid; 3 = oral corticosteroid.

Subjects were asked to record the overall severity of the allergic symptoms on a 10-cm VAS where 0 indicated “no symptoms” and 10 indicated “maximal symptoms” at each visit.

All of the adverse events (AEs) reported during the study period were recorded on a diary card and were promptly addressed under the instruction of the physician based on the following principles: mild local reaction, none; aggravating local reactions/moderate reactions, drug therapy or other treatments as needed, and/or proper delay or reducing of SLIT dose.

Statistical analysis was carried out using SPSS 20.0. All tests were 2-tailed, and the level of significance was set at 0.05. The analysis of variance (ANOVA) or chi-square test was used for a baseline assessment. The statistical significance of difference between baseline and treatment value was determined using the Student *t* test or the nonparametric Mann-Whitney U test or Wilcoxon signed rank test. For those data not conforming to normal distribution law or homogeneity of variance, the Friedman test and *q* test were used for intergroup comparison. All data are shown as mean $\pm$ standard deviation (SD).

Results

This study enrolled 112 children aged 4 to 13 years old with respiratory allergic diseases. There were no significant differences between the 2 groups in age, sex ratio, TASS, TNSS, TMS, VAS, and grade of skin reaction at baseline (all *p* > 0.05; Table 1); 73.21% of the children (41/56) in the monosensitized group and 62.50% of the children (35/56) in the polysensitized group completed the study ($\chi^2 = 1.474$; *p* > 0.05). None of the children withdrew from this study because of AEs.

The TNSS and TASS in all the groups and subgroups significantly improved from week 4 and this improvement was maintained throughout the study period (Fig. 1; all *p* < 0.05). There was no significant difference between the monosensitized group and polysensitized group at each follow-up visit (both *p* > 0.05). Furthermore, there was no significant difference in TNSS and TASS among the monosensitized group, subgroup 1, and subgroup 2 (all *p* > 0.05).

After treatment, a significant reduction of TMS was first found at week 16 in both the monosensitized and polysensitized groups (all *p* < 0.05; Fig. 2), and no significant difference between the monosensitized group and polysensitized group was found throughout the entire study period (all *p* > 0.05). A significant reduction of TMS had been observed after week 12 in subgroup 2 (*p* < 0.05), and at week 20 in the subgroup 1 (*p* < 0.05). No significant difference between subgroup 1 and the monosensitized group was found over the entire study period (all *p* > 0.05), whereas a significant higher TMS was shown at baseline and week 20 in subgroup 2 (*p* < 0.05). There was no significant

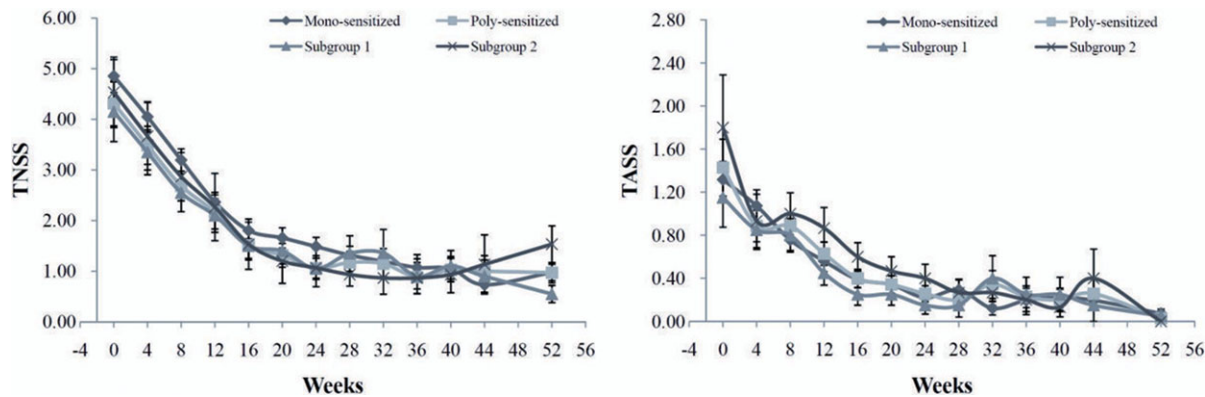


FIGURE 1. The rhinitis and asthma symptoms scores at each follow-up visit. There was no significant difference in TNSS and TASS between groups throughout the study period. TNSS = total nasal symptoms score; TASS = total asthma symptoms score.

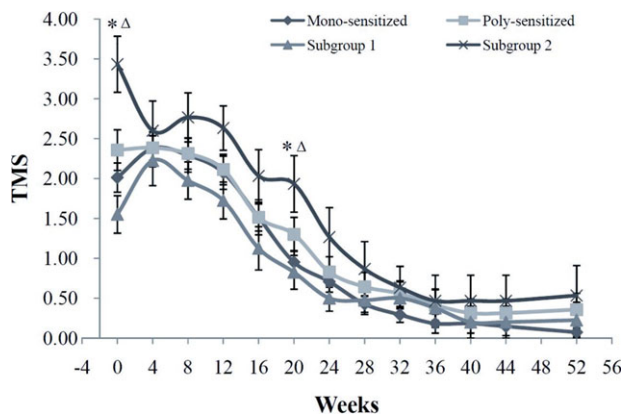


FIGURE 2. The TMS at each follow-up visit. There is was a significant high TMS in the subgroup 2 at week 0 (baseline) and week 20. * $p < 0.05$, compared with the monosensitized group; Δ , $p < 0.05$, compared with subgroup 1. TMS = total medications score.

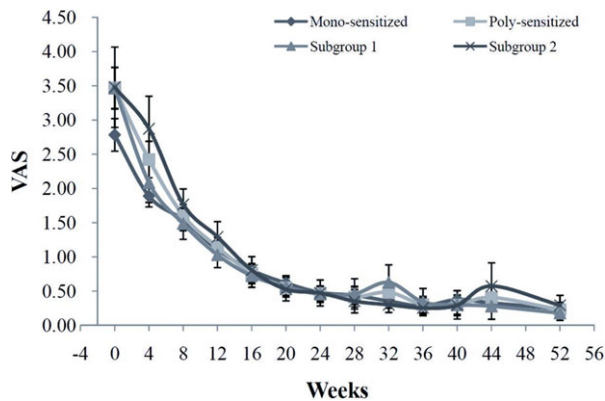


FIGURE 3. The VAS at each follow-up visit. There is no significant difference in VAS between groups throughout the study period. VAS = visual analogue scale.

difference in TMS among the monosensitized group, subgroup 1, and subgroup 2 after week 24 (all $p > 0.05$). VAS in the monosensitized group, polysensitized group, and subgroup 1 significantly declined after week 4 (all $p < 0.05$; Fig. 3). However, VAS in subgroup 2 significantly declined after week 8 ($p < 0.05$).

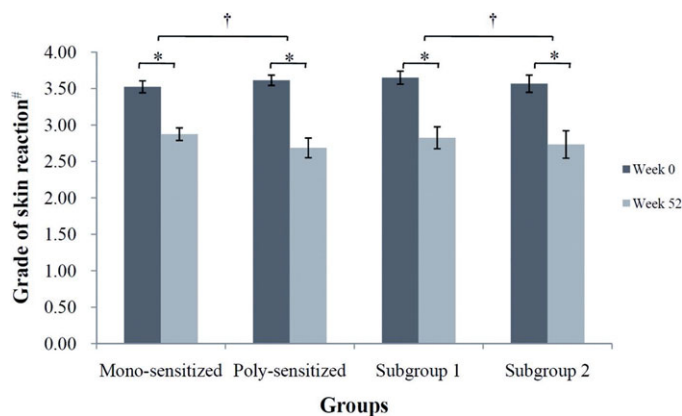


FIGURE 4. The grade of skin reaction before and after treatment. There is no significant difference in skin reaction between groups throughout the study period. #Skin reaction to *D.f.* or *D.p.* or average of skin reactions to *D.f.* and *D.p.*; * $p < 0.05$, compared with week 0 (baseline); † $p > 0.05$, comparison between groups. *D.f.* = *Dermatophagoides farinae*; *D.p.* = *Dermatophagoides pteronyssinus*.

TABLE 2. The percentages of non-dust mite allergens in subgroup 1 and 2(%)

Allergens	Subgroup 1 (%)	Subgroup 2 (%)
<i>Blomia tropicalis</i>	80	93
Pollens	10	0
Cat	5	27
Dog	5	40
<i>Periplaneta americana</i>	0	20

The grade of *D.f.*-induced or *D.p.*-induced skin reaction or the average of *D.f.*-induced and *D.p.*-induced skin reaction in all the groups were significantly decreased at the end of study (all $p < 0.05$; Fig. 4), and there was no significant difference between the groups (all $p > 0.05$). The percentages of non-dust mite allergens in subgroup 1 and subgroup 2 are shown in Table 2.

None of the children required hospitalization or withdrew from the study because of AEs. No severe systemic AEs, anaphylaxis, acute attack of asthma, or use of adrenaline were reported. Ten subjects in the monosensitized group and 7 subjects in the polysensitized group reported AEs ($\chi^2 = 0.210$; $p > 0.05$). All AEs were relieved within a week, with or without medication.

Discussion

SLIT has been widely accepted as an effective and safe administration route for allergen-specific immunotherapy.¹⁴ However, polysensitization has caused many difficulties for allergists prescribing allergen-specific immunotherapy. Determining the clinical efficacy of single-allergen SLIT in polysensitization is becoming increasingly urgent.

This prospective, open-label study focused on this meaningful aspect. The results of our comparative study suggest that there is no significant difference in clinical efficacy and onset time of HDM SLIT between monosensitized subjects and polysensitized subjects (mean number of allergens: 2.71 ± 1.05); we attributed this outcome to possible cross-reactivity of the allergens or to the potential “bystander” effect. The HDM SLIT could not only promote the body to produce immune tolerance to the most clinically relevant allergen HDM, but also activate inducible regulatory T cells, which exert a partially nonspecific immunologic regulatory effect on immune responses even to unrelated antigens.^{15,16} This nonspecific suppression effect of regulatory T cells is called the “bystander” effect. Indeed, evaluating the objective disease parameter specific IgE (sIgE) for the non-HDM allergens of the polysensitized subjects will greatly help to explain the “bystander” effect. However, in this study, we did not limit the polysensitized subjects to the specific allergens (ie, *Blomia tropicalis* or pollens) for the non-HDM allergens; the sIgE for the non-HDM allergens of the polysensitized subjects were not comparable. Improving the inclusion criteria and adding sIgE for the non-HDM allergens will be considered in future work. The SPT results of

polysensitized subjects in our study indicated that *Blomia tropicalis* was the major non-HDM allergen (Table 2), and the high homology and cross-reactivity between HDMs and *Blomia tropicalis* have been proved by immunohistochemical investigations.^{17,18}

We further confirmed that polysensitized subjects may benefit from HDM SLIT as much as monosensitized subjects, and therefore concluded that the sensitization status may not be related to the clinical efficacy of HDM SLIT. This is supported by the present investigation, in which we observed no significant difference in TNSS, TASS, and degree of *D.f.* skin reaction among the monosensitized group, subgroup 1, and subgroup 2 subjects (mean number of allergens: 3.67 ± 0.98). However, the time of significant medication improvements in subgroup 2 subjects seems to be a little earlier than that in the other subjects, which may be explained that subjects sensitive to more than 3 allergens may suffer more serious burden,^{1,19,20} and an increased treatment effect was usually observed in the most severe subjects.²¹ Hence, the faster improvements of TMS in subgroup 2 may result from a significant higher TMS at baseline, and significant difference in TMS among the monosensitized group, subgroup 1, and subgroup 2 would not be observed after week 24. On the other hand, several limitations of this study, such as the small sample size and the polysensitization status in China may be different from other countries should be taken into account for the result analysis.

Conclusion

This prospective, open-label study has suggested that polysensitized subjects may benefit from HDM SLIT as much as monosensitized subjects. The sensitization status may be not related to the efficacy of HDM SLIT, and the effect of SLIT with the most clinically relevant allergen HDM may also be extended to the other allergens. Because this result could have relevant clinical implications, it needs more rigorous confirmation. ☯

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UPCOMING MEETING ANNOUNCEMENT 2014

The 33rd ISIAN meeting (International Society of Inflammation and Allergy of the Nose), in combination with the IRS (International Rhinologic Society) will be held in **Dubai, November 20th to 24th 2014**, under the leadership of Reda Kamel, M.D. This major international meeting promises to bring together rhinologic leaders from around the globe. For more information, please go to <http://isian-irs-pars2014.org/about-dubai.php>