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Letter to the Editor

Effectiveness and safety of subcutaneous immunotherapy with standardized house dust mite extract for patients under the age of 5 years: A prospective cohort study

Dear Editor,

Standardized house dust mite (HDM) allergen extracts are available in Japan for patients requiring subcutaneous immunotherapy (SCIT), however, HDM SCIT for patients aged under 5 years has not been recommended due to the lack of administration experience.¹ To the best of our knowledge, this is the first prospective cohort study to examine the effectiveness and safety of HDM SCIT for patients aged under 5 years.

Patients with allergic rhinitis and/or bronchial asthma, who had specific IgE antibody against *Dermatophagoides*, were included in this study. Rush induction of HDM SCIT (HDM rSCIT) was introduced in 17 patients aged under 5 years (younger group) and 45 patients aged 5 years and above (older group); the treatment was maintained for one year in both the groups. The patients were hospitalized during HDM rSCIT and administered 500 Japanese allergy units (JAU) of HDM once a month in the outpatient clinic during the maintenance phase (Supplementary Table 1).² In patients who developed a systemic reaction (SR) during HDM rSCIT, the dose was increased to 500 JAU using the conventional method. We evaluated the difference in SRs of HDM SCIT between the two groups during the entire study period. Swelling and/or erythema at the injection site were regarded as local reactions, and the major axis of wheal was measured 30 min after each injection. Allergic symptoms, except for local reactions, were regarded as SRs and evaluated using the Grade classification.³ Further, bronchial asthma and allergic rhinitis symptoms were evaluated using the pediatric bronchial asthma treatment scores (PBATS) and allergic rhinitis symptom medication score (ARSMS), respectively.^{4,5} The effectiveness of HDM SCIT was assessed by comparing the PBATS and ARSMS before and after HDM rSCIT (at 1, 3, 6, and 12 months). Proportions and median values were compared using Fisher's exact test and Mann–Whitney U test. The median values of PBATS and ARSMS were compared using the Wilcoxon signed-rank test, due to skewed distributions. *P*-values < 0.05 were considered statistically significant. For multiple comparisons of paired data between the baseline values and those at 1, 3, 6, and 12 months after treatment, the *p*-values were adjusted using the Bonferroni correction. Written informed consent for study participation and reporting of the results was obtained from participants' parents. This study was approved by the Yao Municipal Hospital Ethics Committee (YMH-092820-93).

A history of food allergy was significantly more common in the younger group (*p* = 0.019), whereas the older group had significantly higher PBATS (*p* = 0.026) (Table 1). All patients experienced local reactions. There was no significant difference in the major axis of wheal 30 min after injection at the time of between one step before the appearance of SR and SR appearance (1.97 ± 1.28 cm, 2.03 ± 1.07 cm, *p* = 0.773). There was no significant difference in

Table 1
Baseline characteristics of patients.

Characteristics [†]	Younger group <5 years (n = 17)	Older group ≥5 years (n = 45)	<i>p</i> -value
Male, n (%)	12 (70.6)	31 (68.9)	1.00
Age, median (IQR)	3.0 (3–4)	7.0 (6–9)	<0.001
Prevalence of bronchial asthma, n (%)	17 (100.0)	44 (97.8)	1.00
Mild, n (%)	12 (70.6)	22 (50.0)	
Moderate, n (%)	3 (17.6)	6 (13.6)	
Severe, n (%)	2 (11.8)	16 (36.4)	
PBATS, median (IQR)	150 (120–300)	300 (143–630)	0.026
Prevalence of allergic rhinitis, n (%)	17 (100.0)	41 (91.1)	0.568
Mild, n (%)	6 (35.4)	6 (14.6)	
Moderate, n (%)	3 (17.6)	19 (46.4)	
Severe, n (%)	5 (29.4)	8 (19.5)	
Most Severe, n (%)	3 (17.6)	8 (19.5)	
ARSMS, median (IQR)	4 (2–5)	5 (3–5)	0.281
Season in which HDM rSCIT was introduced, n (%)			
Spring (March–May)	3 (17.6%)	6 (13.3%)	0.502
Summer (June–August)	6 (35.3%)	25 (55.6%)	
Autumn (September–November)	2 (11.8%)	4 (8.9%)	
Winter (December–February)	6 (35.3%)	10 (22.2%)	
Patients with atopic dermatitis, n (%)	16 (94.1)	38 (84.4)	0.427
Patients with Type 1 food allergy, n (%)	15 (88.2)	25 (55.6)	0.019
Total IgE titer (IU/mL), median (IQR)	675.0 (176.0–1554.3)	591.5 (291.2–1236.8)	0.772
Specific IgE titer, median (IQR)			
<i>Dermatophagoides pteronyssinus</i> (IUA/mL)	110.0 (29.5–122.0)	65.6 (34.7–125.0)	0.950
<i>Dermatophagoides farinae</i> (IUA/mL)	132.0 (34.0–203.0)	100.0 (61.0–203.0)	0.922

PBATS, pediatric bronchial asthma treatment score; ARSMS, allergic rhinitis symptom medication score; n, number of patients; IQR, interquartile range; HDM, standardized house dust mite; rSCIT, rush induction of subcutaneous immunotherapy.

[†] Baseline characteristics of patients were evaluated at the time of study enrollment.

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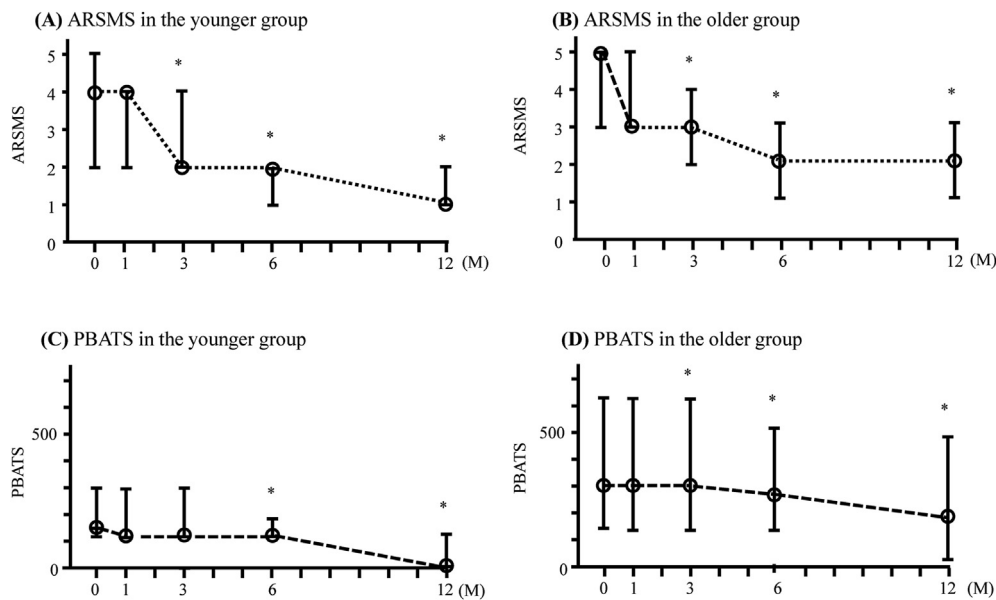


Fig. 1. Allergic rhinitis symptom medication score (ARSMS) and pediatric bronchial asthma treatment score (PBATS) before and 1, 3, 6, and 12 months after initiating HDM SCIT. Circles and error bars show medians and interquartile range, respectively. The median ARSMS was 4 and 1 points in the younger group (A), and 5 and 2 points in the older group (B) before and 1 year after initiating HDM SCIT, respectively. The median PBATS was 150 and 0 points in the younger group (C), and 300 and 180 points in the older group (D) before and 1 year after initiating HDM SCIT, respectively. **p* was less than 0.05. ARSMS, allergic rhinitis symptom medication score; PBATS, pediatric bronchial asthma treatment score; HDM SCIT, subcutaneous immunotherapy using standardized house dust mite allergen extract; younger group, patients under 5 years of age; older group, patients aged 5 years and above; M, months.

the incidence of SRs between the younger and older groups during increased period up to 500 JAU (58.8% vs. 64.4%, $p = 0.771$) and maintenance phase (11.8% vs. 17.8%, $p = 0.713$) (Supplementary Table 2).² There was no significant difference in the incidence of Grade 3 SRs between the two groups during increased period up to 500 JAU (5.9% vs. 6.7%, $p = 1.000$). One patient in the younger group and three patients in the older group developed Grade 3 SRs, all others developed $\leq$ Grade 2 SRs. Among the Grade 3 SRs, three patients experienced respiratory symptoms requiring oxygen administration, and one patient experienced abdominal symptom requiring steroid administration. In patients who developed SRs during HDM rSCIT, the dose was increased to 500 JAU using the conventional method. All patients could continue HDM SCIT. In both groups, ARSMS decreased significantly 3 months after HDM rSCIT. PBATS decreased significantly after 6 months in the younger group, and after 3 months in the older group. At 12 months after HDM rSCIT, the median ARSMS decreased significantly from 4 to 1 point ($p < 0.001$) in the younger group, and from 5 to 2 points ($p < 0.001$) in the older group (Fig. 1). Similarly, the median PBATS in the younger group decreased significantly from 150 to 0 points ($p = 0.011$) in the younger group, and from 300 to 180 points ($p < 0.001$) in the older group (Fig. 1).

This is the first study reporting the effectiveness and safety of HDM SCIT for patients aged under 5 years. A previous study has reported the effectiveness and safety of HDM SCIT, however, it did not include patients aged under 5 years.¹ Another immunotherapy study that included younger individuals used a non-standardized HDM allergen extract.⁶ A randomized control study, including 300 children aged between 3.5 and 7.5 years, reported the effectiveness and safety of SCIT using HDM or pollen extract, however, the study did not report HDM use alone.⁷ According to the joint task force report for allergen immunotherapy (AIT), AIT can be initiated for patients aged under 5 years, but a proper assessment of the benefits and risks is a prerequisite.⁸

In this study, PBATS in the older group was higher than that in the younger group. AIT is a treatment capable of altering the natural

course of allergic disease. Therefore, early introduction of HDM SCIT at a younger age may be beneficial for the highly variable immune system.⁹

The incidence of SRs during increased period up to 500 JAU was higher in both groups than in previous reports.⁷ The previous study reported a higher incidence of SRs among patients with rapid dose escalation up to 500 JAU (85.7%) compared with those with escalation up to 200 JAU (30.0%).¹⁰ Consistently, we reported that rapid dose escalation up to 500 JAU caused SRs in 40 of 51 patients (78.4%), whereas rapid dose escalation up to 300 JAU followed by conventional dose escalation to 500 JAU reduced SRs in 4 of 17 patients (22.2%).² The reason for the high incidence of SRs in this study was due to the dose being over the target dose during HDM rSCIT. We believe that the incidence of SRs can reach acceptable levels by reduction of the target dose during HDM rSCIT. Further investigation of the appropriate maintenance dose of HDM SCIT that is acceptable in terms of both safety and therapeutic effect is required.

There are some limitations in this study. There was no control group to compare the effectiveness of HDM SCIT. Due to the small sample size, we were unable to adjust for the confounding factors such as PBATS, ARSMS, and a history of food allergy.

In conclusion, this study showed that HDM SCIT was effective for patients with allergic rhinitis and bronchial asthma aged under 5 years, albeit with safety issues.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.05.004>.

Conflict of interest

The authors have no conflict of interest to declare.

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