Efficacy and safety of house dust mite subcutaneous immunotherapy in polysensitized children with allergic asthma

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Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4249980

Abstract

Introduction: The aim of this study was to compare the efficacy and safety of 3 years of HDM subcutaneous immunotherapy (HDM-SCIT) in allergic asthma (AA) children with mono- and polysensitized.

Methods: This was a retrospective observational study, 51 AA children (aged 4-14 years) who had completed 3 years of standardized HDM-SCIT were enrolled in. Based on skin prick tests (SPT) and allergen-specific IgE antibody (sIgE) test results, children were classified into two groups: the monosensitized group (n=31) and the polysensitized group (n=20). Total asthma symptoms score (TASS), total medication score (TMS), visual analog scale (VAS) scores, lung function parameters, fractional exhaled nitric oxide (FeNO), and adverse reactions were evaluated before treatment and at 6 months, 1, 2, 3 years of HDM-SCIT.

Results: In terms of effectiveness, compared to baseline, TASS, TMS, VAS, FeNO and lung function parameters were significantly improved in both groups after 3 years of HDM-SCIT (all $P<0.05$). The comparison between the two groups showed that all efficacy indicators were no statistically significant difference at all follow-up time points (all $P>0.05$). In terms of security, the number of adverse reactions in both groups also no statistical difference between the two groups (all $P>0.05$).

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Conclusion: This study confirmed that there was no significant difference observed in the clinical efficacy and safety of HDM-SCIT between mono-and polysensitized children with allergic asthma.

Keywords: Subcutaneous immunotherapy; House dust mite; Polysensitized; Allergic asthma; Children

Introduction

Allergic asthma (AA) is one of the most common respiratory allergic diseases, currently affecting more than 300 million people worldwide including children[1]. AA is commonly associated with recurrent wheezing, coughing, chest tightness, difficulty breathing and increased mucus production[2]. These symptoms are often caused by aeroallergen, especially house dust mite (HDM) [3]. More than 50% of children and teens with asthma are sensitive to HDM[4].

HDM induces AA by stimulating the CD4+ T cells of genetically susceptible individuals to produce IL-4, IL-5, IL-13 and to promote the differentiation of Th2 and Th17[5]. Dermatophagoides pteronyssinus (D.p) and Dermatophagoides farina (D.f) are the most important types of HDM, which account for more than 90% of the world's HDM-related allergies diseases [6, 7]. Allergies caused by HDM usually start in childhood and last through puberty and develop into other serious illnesses in adulthood.

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Allergy-specific immunotherapy (AIT) is the only etiologic treatment that induces T and B lymphocytes to tolerate allergens, reduces allergic reactions and improves the quality of life[8-10]. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the most common routes of clinical administration[11]. AIT has been well documented to be efficacious in monosensitization patients (only one type of allergen) with allergic disease [12-15], but patients with polysensitization (> one type of allergen) may not be as successfully treated by AIT as patients with monosensitization[16]. Actually, patients with polysensitization make up a large proportion of people with allergies and those patients often have a more urgent desire to improve their quality of life [17-19]. Therefore, it has clinically important to understand the efficacy and safety of AIT in patients with polysensitization. Recent clinical trials have indicated that HDM single-agent immunotherapy is safe and effective in treating polysensitized allergic rhinitis (AR) through AIT[20, 21].

However, there are no long-term clinical studies on whether HDM AIT especially SCIT will be clinically efficacious and safe for children with allergic asthma who are polysensitized. Therefore, the purpose of this study is to compare the efficacy and safety of house dust mite subcutaneous immunotherapy (HDM-SCIT) in mono- and polysensitive asthmatic children.

2. Materials and Methods

Patients

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This was a retrospective observational study. Children who were AA with or without allergic rhinitis (AR) were admitted. The inclusion criteria were as follows: (1) aged between 4 and 14; (2) diagnosed with mild to moderate allergic asthma according to criteria described by Global Initiative for Asthma (GINA) guidelines; (3) $FEV_1 >$ 70% of the predicted value; (4) positive SPT of D.p and/or D.f; (5) D.p and/or D.f IgE $\geq$ 0.35 IU/ml; (6) asthma symptoms after exposure to D.p and/or D.f; (7) completed 3 years of HDM-SCIT between May 2007 and Aug 2021 in the Department of Pediatrics, Xijing Hospital. The children who have severe asthma or nonallergic autoimmune disease, chronic infection, tumor, severe cardiovascular disease and mental disorders were excluded from this study.

SPT was performed by trained nurses in our center and the results were evaluated by physicians. The standard aeroallergen panel including HDMs (D.p and D.f), Blatella germanica, Periplaneta americana, Artemisia vulgaris, ragweed, Dog dander, Cat dander, Mould mix I (Fusiorum moniliforme, Cladosporium herbarum, Alternaria alternata), Mould mix II (Niger, Aspergilllus fumigatus), mixed grasses(Lolium perenne, Festuca pratensis, Dactylis glomereta, Poa pratensis, Phleum pratense,) and mixed trees (Coryllus avellana, Alnus glutinosa, Betula verrucosa) (ALK-Abelló, Denmark). physiologic saline was used as negative control and histamine was used as the positive control. Wheal size was measured after 20 minutes. The average wheal diameter was calculated according to the (d + D)/2 formula, in which d was the maximum horizontal diameter and D was the largest longitudinal

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diameter. The average wheal size of ≥3mm was defined as positive. All patients were instructed not to take antihistamines during the one week before the test. Allergen-specific IgE (sIgE) test was measured using the Allergy Screen test panel (Mediwiss Analytic, Moers, Germany), and the level of sIgE ≥ 0.35 IU/ml was defined as positive.

Based on SPT and sIgE test results, children were classified into two groups: monosensitized (allergic only to D.p and/or D.f) and polysensitized (allergic to D.p and/or D.f as well as other allergens). The total asthma scores(TASS), total medication scores(TMS), visual analog scale(VAS) score, fractionated exhaled nitric oxide (FeNO) , lung function parameters and adverse reactions were collected before SCIT（baseline ）and at 6 months, 1, 2, 3 years of SCIT. This research was performed in accordance with the World Medical Association Declaration of Helsinki and has been granted an exemption from requiring ethics approval by the committee of Xijing Hospital of Fourth Military Medical University, Xi'an, China. Oral informed consent was obtained from all parents.

Subcutaneous immunotherapy (SCIT)

SCIT was performed with a standardized extract of HDM (ALK-Abelló, Denmark). Treatment consists of two stages: initiation and maintenance. The first 15 weeks are the initial stage of treatment (dosing increasement phase), administration of minimal doses and gradually increasing in the order of vials 1, 2, 3 and 4 to maintain the dose of 100,000 SQ-U (1.0 ml) or the maximum tolerated dose. The maintenance

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stage was the maximum dose of antigen injections 2-4 weeks gradually adjusted to 6-8 weeks until the end. Patients should stay for at least 30 minutes to prevent unexpected events. Adverse reactions should be addressed and recorded in a timely manner, adjusting the dose as necessary. All injections were performed by the nurses at the Department of Pediatrics, Xijing hospital.

Clinical efficacy score

Total asthma symptoms score (TASS)

TASS was the sum total of daytime and night asthma symptom scores. asthma symptoms range from 0 to 5 during the daytime, depending on the severity of clinical symptoms, including wheezing, coughing, chest tightness, shortness of breath and their impact on daily life. 0=asymptomatic; 1=less symptomatic and a short duration; 2=two or more symptomatic and a short duration; 3=mild symptomatic for long periods of time throughout the day and less impact on life and work; 4=severe symptomatic for long periods of time throughout the day and impact on life and work; 5=severe symptoms that the children could not engage in studying and normal living. Night asthma symptoms range from 0 to 4 depending on how often the asthmatic wakes up at night and early morning awakening due to asthma, 0=asymptomatic; 1= wake up once or early; 2=wake up 2 times, including early awakening; 3=wake up multiple times;4=difficulty to fall asleep at night

Total medication score (TMS)

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All patients were prescribed antiallergic drugs, including oral or topical antihistamine, antileukotrienes, β_2-agonists and an oral or topical corticosteroid. TMS was evaluated based on daily dosing of symptomatic drugs: 0=none; 1=β2-agonists or orantihistamine or antileukotrienes; 2=inhaled corticosteroid; 3=oral corticosteroid.

visual analog scale (VAS)

Patients were asked to record the severity of their allergic asthma symptoms on a scale of 0-10, 0 indicating asymptomatic and 10 indicating the most severe.

FeNO and Lung function test

FeNO was measured using Sunvon (Wuxi, China),the measured values were expressed in parts per billion (ppb) according to international recommendations [32]. Lung function tests were measured using a spirometer (PowerCube, Germany), children performed at least two comparable flow-volume curves, or three forced expiratory maneuvers starting in the maximum inspiratory position to obtain the best FEV_1, FVC, PEF and MMEF values, and recorded it as a percentage of the expected value. FeNO and lung function tests were performed every time before SCIT treatment.

Safety

Throughout the treatment, adverse reactions were recorded timely after each SCIT injection, including local reactions and system reactions. Erythema and/or swelling and/or itching at the injection area were defined as local reactions, nasopharyngitis,

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wheezing, urticariaone and other organ system symptom were classified into system reactions according to the AIT Systemic Reaction Grading System proposed by WAO[22].

Statistical Analyses

Statistical analysis was performed by SPSS 26.0 software. Continuous variables were reported as mean± SD, intergroup comparison using Student t test if normality is met, or Mann-Whitney U test if not normality, and repeated-measurements analysis of variance was used to compare intragroup differences at 5 different time points (baseline, 6 months, 1, 2, 3 years). Count data were reported as n (%), intergroup comparison using the chi-square test or Fisher's exact test between groups, and the Bonferroni correction method was used to compare intragroup differences. $P< 0.05$ was considered statistically significant.

Results

Baseline characteristics of the children

This study included 51 AA children (39 males and 12 females) with an average age of 8.42 ± 2.29 years (range 4-14 years). Combining their SPT and sIgE testing results, children were divided into two groups: monosensitized (n=31) or polysensitized(n=20). The two groups were comparable for all demographic characteristics except FEV1%pred (P=0.016). The demographic and clinical characteristics of the children are summarized in Table 1. Among polysensitized group,

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we further analyzed the proportion of specific allergens of these children. The most common positive allergens were Dog dander (45%), Cat dander (40%), and Artemisia vulgaris (25%) (Table 2).

Table 1. Patient characteristics in the monosensitized and polysensitized groups

Characteristics	Monosensitized group(n=31)	Polysensitized group(n=20)	t /χ2/z	*P*-value
Age（years）	8.20±2.31	8.74±2.29	*t* =-0.827	NS
D.p（diameter，mm）	9.13±8.29	7.43±2.95	*t* =0.882	NS
D.f（diameter，mm）	7.73±3.57	8.68±3.23	*t* =-0.948	NS
M/F（n）	25/6	14/6	*χ2*=0.288	NS
AA alone/AA+AR（n）	13/18	11/9	*χ2*=0.833	NS
TASS	3.32±1.56	3.50±1,67	*z*=-0.884	NS
TMS	3.77±1.61	3.30±0.92	*z*=-0.765	NS
VAS	5.77±1.52	6.15±1.39	*t* =-0.891	NS
FeNO	27.35±10.90	29.55±10.60	*t* =-0.710	NS
FVC %pred	88.58±3.15	87.75±3.23	*t* =0.911	NS
FEV_1%pred	73.65±2.36	75.40±2.56	*t* =-2.507	*P*=0.016
PEF %pred	85.19±4.33	84.55±5.69	*t* =0.458	NS
MMEF %pred	60.13±16.58	65.80±16.32	*t* =-1.200	NS

Abbreviations: M = male; F = female; AA=allergic asthma; AR=allergic rhinitis; D.p= D.pteronyssinus; D.f=D. farina; TASS=total asthma scores;TMS= total medication scores;VAS= visual analog scale; FeNO=Fractionated exhaled nitric oxide; FVC%pred=Forced vital capacity in percentage of predicted value; FEV1%pred=Forced expiratory volume in one second in percentage of predicted value; PEF%pred=Peak expiratory flow in percentage of predicted value; MMEF%pred=Maximum midexpiratory flow in percentage of predicted. t represents intergroup comparison using Student t test. χrepresents intergroup comparison using chi-square test； z represents intergroup comparison using Mann-Whitney U test. NS：there were no significant differences among the two group.

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Table 2. The proportion of specific allergens causing mono-or polysensitized allergic asthma（n,%）

Allergen	Monosensitized group (n=31)	Polysensitized group (n=20)
D.p	31(100%)	20(100%)
D.f	30(96.8%)	20(100%)
D.p+D.f	30(96.8%)	20(100%)
Dog dander	-	9（45%）
Cat dander	-	8（40%）
Artemisia vulgaris	-	5（25%）
Ragweed	-	4（20%）
Mould mix I	-	4（20%）
Mixed grasses	-	3（15%）
Blatella germanica	-	2（10%）
Mould mix II	-	1（5%）
Periplaneta americana	-	1（5%）

n：positive cases, %：positive in each group patients; D.p= D.pteronyssinus; D.f=D. Farina

Mould mix I including Fusiorum moniliforme, Cladosporium herbarum and Alternaria alternata;Mould mix II including Niger and Aspergilllus fumigatus.

Clinical efficacy score

The results of the comparison of TASS, TMS and VAS score before and after 6 months, 1, 2, 3 years of HDM-SCIT in the mono- and polysensitized groups were shown in Figure1 and Table 3. Compared to baseline, TASS, VAS in both groups and TMS in monosensitized group improved significantly after 6 months of treatment and remained improved throughout the study period (all $P < 0.05$). At 6 months, 1, 2, 3

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years of HDM-SCIT, TASS of polysensitized group were 1.70±1.17, 1.00±1.12, 0.65±1.09 and 0.45±1.05 respectively, compared with the monosensitized group, no statistical difference between the two groups at all follow-up time points (z=-0.540, -0.993,- 0.661, -0.121, all P>0.05); TMS of polysensitized group were 2.70±0.57, 2.50±0.76, 1.55±0.95 and 1.15±1.09 respectively, compared with the monosensitized group, no statistical difference between the two groups at all follow-up time points (z=-0.547, -0.502, -0.274, -0.495, all P>0.05); VAS of polysensitized group were 3.75±1.16, 2.85±1.27, 1.95±0.83 and 1.80±0.95 respectively, compared with the monosensitized group, no statistical difference between the two groups at all follow-up time points (z=-0.766, -1.157, -1.309, -0.961, all P>0.05).

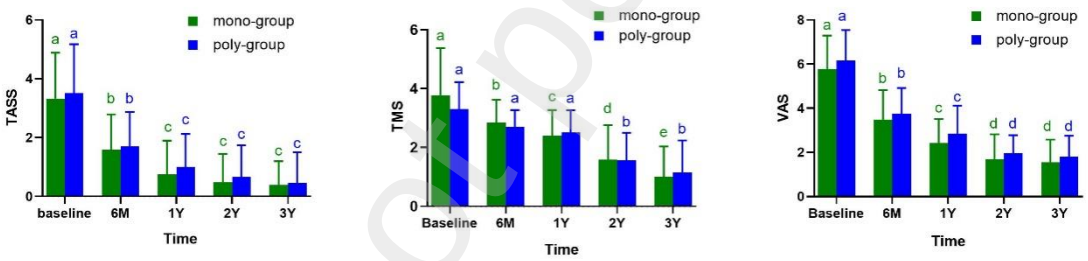

Figure 1. Comparision of TASS, TMS and VAS between the mono-and polysensitized groups at each follow-up visit.

TASS=total asthma symptoms score; TMS=total medication score; VAS=visual analog scale. a b c d e is the letter notation method for the comparison between each time point within the group. Comparison between groups using the Mann-Whitney U test. There were no signifificant difference in TASS, TMS and VAS between groups at all time points.

FeNO and Lung function test

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The results of the comparison of FeNO and lung function parameters before and after 6 months, 1, 2, 3 years of treatment in the mono- and polysensitized groups were shown in Figures 2, 3 and Table 3. Compared to baseline, FeNO and all parameters of lung function were significantly improved in both groups after 6 months and the improvement was also maintained throughout the study period (all P<0.05). At 6 months, 1, 2, 3 years of HDM-SCIT, FeNO of polysensitized group were 18.20±4.94, 15.15±3.36, 13.10±3.35 and 13.10±2.63 respectively, compared with the monosensitized group, no statistical difference between the two groups at all follow-up time points (z=-1.500,-1.553,-0.029,-0.446, all P>0.05); lung function test including FVC%pred, FEV1%pred, PEF%pred and MMEF%pred, all of the parameters were no significant differences between the two groups at each follow-up visit (all P >0.05).

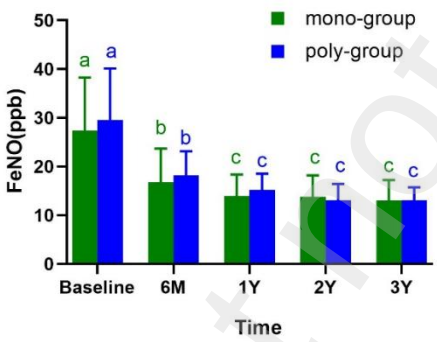

Figure 2. Comparision of FeNO between the mono-and polysensitized groups at each follow-up visit.

FeNO=Fractional exhaled nitric oxide. a b c is the letter notation method for the comparison between each time point within the group. Comparison between groups using the Mann-Whitney U test. There were no signifificant difference between groups at all time points.

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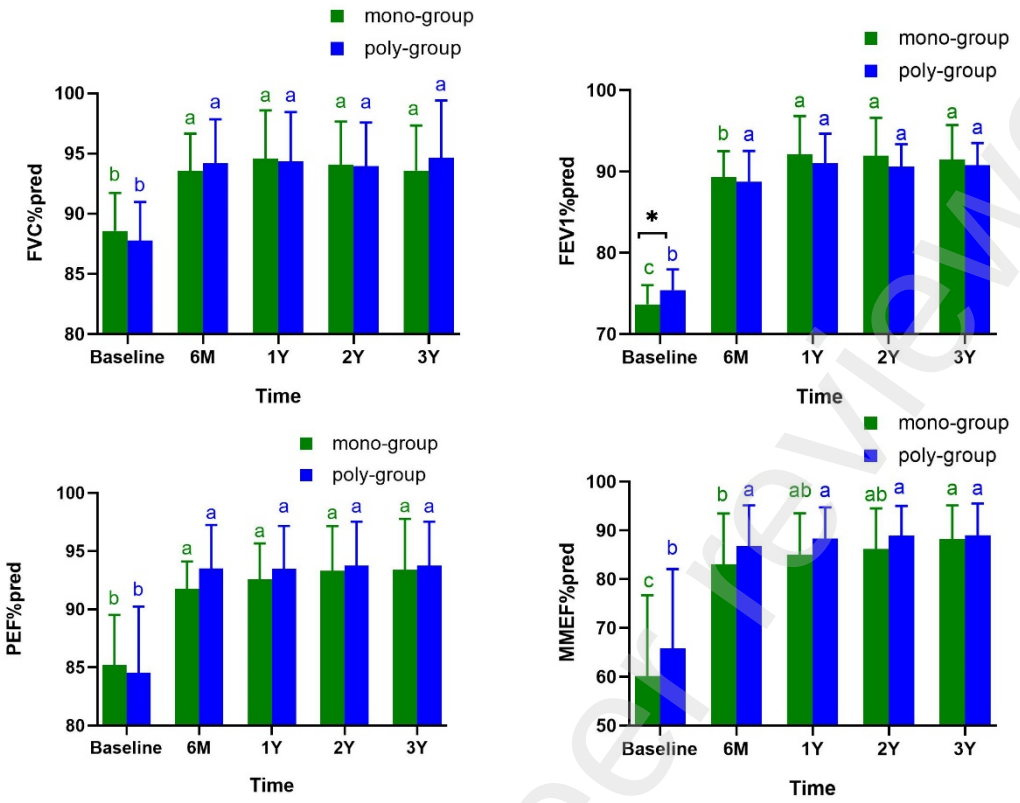

Figure 3. Comparision of lung function parameters between the mono-and polysensitized groups at each follow-up visit.

FVC%pred=Forced vital capacity in percentage of predicted value; FEV1%pred=Forced expiratory volume in one second in percentage of predicted value; PEF%pred=Peak expiratory flow in percentage of predicted value; MMEF%pred=Maximum midexpiratory flow in percentage of predicted. a b c is the letter notation method for the comparison between each time point within the group. Comparison between groups using the Mann-Whitney U test. Except for FEV1%pred at baseline, there were no significant differences between the two groups in other time points.

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Table 3. Comparison of Clinical efficacy score, FeNO and lung function parameters before and during SCIT for children with allergic asthma in the mono- and polysensitized groups.

	Baseline				6 Months				1 year				2 years				3 years			
	Mono-	Poly-	z	P-value	Mono-	Poly-	z	P-value	Mono-	Poly-	z	P-value	Mono-	Poly-	z	P-value	Mono-	Poly-	z	P-value
TASS	3.32±1.56	3.50±1.67	-0.884	0.377	1.58±1.20	1.70±1.17	-0.540	0.589	0.74±1.15	1.00±1.12	-0.993	0.321	0.48±0.96	0.65±1.09	-0.661	0.509	0.39±0.80	0.45±1.05	-0.121	0.904
TMS	3.77±1.61	3.30±0.92	-0.765	0.444	2.84±0.78	2.70±0.57	-0.547	0.585	2.39±0.88	2.50±0.76	-0.502	0.615	1.58±1.18	1.55±0.95	-0.274	0.784	1.00±1.03	1.15±1.09	-0.495	0.621
VAS	5.77±1.52	6.15±1.39	-0.934	0.350	3.48±1.34	3.75±1.16	-0.766	0.444	2.42±1.09	2.85±1.27	-1.157	0.247	1.68±1.34	1.95±0.83	-1.309	0.191	1.55±1.—0.	1.80±0.95	-0.961	0.336
FeNO	27.35±10.90	29.55±10.60	-0.801	0.423	16.74±6.95	18.20±4.94	-1.500	0.134	13.90±4.44	15.15±3.36	-1.553	0.120	13.71±4.47	13.10±3.35	-0.029	0.977	13.03±4.20	13.10±2.63	-0.447	0.656
FVC%pred	88.58±3.15	87.75±3.23	-0.515	0.606	93.55±3.11	94.20±3.64	-0.844	0.399	94.58±3.99	94.35±4.10	-0.194	0.846	94.06±3.61	93.95±3.62	-0.107	0.915	93.58±3.74	94.65±4.76	-0.708	0.479
FEV1%pred	73.65±2.36	75.40±2.56	-2.436	0.015*	89.32±3.20	88.75±3.80	--0.601	0.548	92.13±4.70	91.05±3.61	-0.476	0.634	91.97±4.64	90.60±2.76	-0.544	0.587	91.45±4.27	90.80±2.71	-0.097	0.923
PEF%pred	85.19±4.33	84.55±5.69	-0.301	0.763	91.77±2.33	93.50±3.76	-1.517	0.129	92.58±3.10	93.45±3.72	-0.855	0.392	93.32±3.83	93.75±3.80	-0.650	0.516	93.39±4.39	93.75±3.80	--0.690	0.490
MMEF%pred	60.13±16.58	65.80±16.32	-1.083	0.279	83.10±10.37	86.80±8.36	-1.447	0.148	85.00±8.54	88.30±6.42	-1.366	0.172	86.19±8.32	88.95±6.07	-1.017	0.309	88.23±6.91	89.00±6.52	-0.589	0.556

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TASS=total asthma symptoms score; TMS=total medication score; VAS=visual analog scale; FeNO=Fractionated exhaled nitric oxide; FVC%pred=Forced vital capacity in percentage of predicted value; FEV1%pred=Forced expiratory volume in one second in percentage of predicted value; PEF%pred=Peak expiratory flow in percentage of predicted value; MMEF%pred=Maximum midexpiratory flow in percentage of predicted.

Comparison between groups using the Mann-Whitney U test

* Compared between mono- and polysensitized groups, $P < 0.05$.

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Safety Assessment

All the children had different degrees of adverse reactions during treatment administration, but no severe systemic adverse reactions were reported during the treatment in both group. During the first year, 30 patients (96.8%) in the monosensitized group had local adverse reactions,18 patients experienced systemic adverse reactions;19 patients (95.0%) in the polysensitized group had local adverse reactions,11 patients experienced systemic adverse reactions. During the second year, 28 patients (90.3%) in the monosensitized group had local adverse reactions, 7 patients experienced systemic adverse reactions;17 patients (85.0%) in the polysensitized group had local adverse reactions, 5 patients experienced systemic adverse reactions. During the third year, 26 patients (83.9%) in the monosensitized group had local adverse reactions, 7 patients experienced systemic adverse reactions,18 patients (90.0%) in the polysensitized group had local adverse reactions, 2 patients experienced systemic adverse reactions. The most common local side effects were local wheal, swelling and itching, the most common systemic adverse reactions were nasopharyngitis, wheezing, chest tightness, coughing, urticaria, fever and eyelid swelling. All children were relieved by themselves or by medication, and no epinephrine rescue events occurred.The patients number of adverse reactions in the two groups in different treatment periods was shown in Table 4. Except that the number of coughing in the

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monosensitized group was significantly higher than that in the polysensitized group during the second year of treatment (3 vs 1, P=0.030), there was no statistical difference between the two groups during the three years treatment period, whether it was local adverse reactions or systemic adverse reactions (all $P > 0.05$).

Table 4. The number of children about local and system adverse reactions in the monosensitized and polysensitized groups (n, %)

Adverse reaction	1 year			2 years			3 years		
	Monosensitized n=31	Polysensitized n=20	P-Value	Monosensitized n=31	Polysensitized n=20	P-Value	Monosensitized n=31	Polysensitized n=20	P-Value
Local wheal, swelling, itching	30(96.8)	19（95）	0.392	28（90.3）	17（85.0）	0.540	26（83.9）	18（90.0）	0.272
Nasopharyngitis	9（29.0）	2（10.0）	0.166	0（0.0）	1（5.0）	1.000	2（6.5）	0（0.0）	0.103
Wheezing	2（6.5）	3（15.0）	0.369	2（6.5）	2（10.0）	0.103	1（3.2）	1（5.0）	0.333
Chest tightness	2（6.5）	1（5.0）	1.000	0（0.0）	1（5.0）	1.000	1（3.2）	0（0.0）	0.333
Coughing	2（6.5）	4（20.0）	0.195	3（9.7）	1（5.0）	0.030*	1（3.2）	1（5.0）	0.333
Urticaria	3（9.7）	0（0.0）	0.271	1（3.2）	0（0.0）	0.333	1（3.2）	0（0.0）	0.333
Fever	0（0.0）	1（5.0）	0.392	0（0.0）	0（0.0）	1.000	0（0.0）	0（0.0）	1.000
Eyelid swelling	0（0.0）	0（0.0）	1.000	1（3.2）	0（0.0）	0.333	1（3.2）	0（0.0）	0.333

Fisher's exact test to compared between groups;

* Compared between mono- and polysensitized groups, $P < 0.05$.

Discussion

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Most of the previous studies have explored the efficacy and safety of HDM-SCIT in allergic asthma with monosensition, or compared the efficacy of HDM-SLIT in allergic rhinitis between mono- and polysensitivity [23-27]. While our research mainly compared the efficacy and safety of HDM-SCIT between mono- and polysensitized asthmatic children. Symptoms caused by AA are the main cause of quality of life. Therefore, the primary therapeutic goal of AA therapy is ongoing remission based on symptom assessment. TASS, TMS and VAS are the three main evaluation indicators for evaluating treatment efficacy.

In our study, we observed significant improvement in TASS, TMS and VAS among children with polysensitized after 3 years of treatment compared with the baseline, similar to monosensitized children. Although the intergroup comparison did not show statistical differences at all treatment time points, there were some differences in the decreasing trend of TMS between the two groups. TMS in the monosensitized group decreased significantly after 6 months of HDM-SCIT, while the polysensitivity group did not show significant improvement until 2 years of treatment. These results are in line with those of Xie et al [28], they compared the efficacy of the HDM-SLIT in allergic rhinitis between mono- and poly-sensitized children, and found that all parameters in the monosensitized group were equivalent to the polysensitized group, except the TMS was slightly lower than the polysensitized group at 6 months. These results indicated that the symptom relief in the polysensitized group was later than that

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in the monosensitized group, which may be related to the delayed action of the polysensitized patients.

FeNO is commonly used to evaluate the severity of airway inflammation in clinical practice and pulmonary function test is one of the objective indicators reflecting the pathophysiological changes in the airway. They are increasingly applied to evaluating asthma patients due to their non-invasive characteristics [29, 30]. Our research showed that after 6 months of HDM-SCIT, FeNO in the two groups decreased significantly, and the decrease in the polysensitized group was much more than that in the monosensitized group, which may be related to the higher baseline levels of FeNO in the polysensitized group. All parameters of lung function significantly improved after 3 years of treatment. The improvement mainly occurred within 6 months of treatment, and there was a slight improvement in lung function parameters between 6 months and 3 years, with no statistical difference between mono- and polysensitized groups.

In our study, there was no statistically significant difference in the incidence of adverse reactions between the two groups at each time period. HDM-SCIT was generally well tolerated, and while each child had different degrees of adverse reactions, most were mild and localized, this outcome is consistent with the study by DeCastro et al[31] The number of adverse reactions in the two groups decreased significantly with the prolongation of treatment time, especially during the first year. Ma et al showed that the incidence of adverse reactions was significantly lower after

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three years of AIT in the monosensitivity group and polysensitivity group than after the first year[32]. Our study showed that the number of adverse reactions in both groups decreased year by year, especially system adverse reaction, and there was no statistical difference between the two groups.

The efficacy of HDM-SCIT in polysensitized patients may be also associated with cross-reactivity to allergens[33]. In general, cross-reactivity appears to require more than 70% sequence recognition, while proteins with < 50% sequence recognition rarely cross-react[34]. Santos et al[35] found that periplaneta americana tropomyosin had 80% and 81% sequence identity to tropomyosins from D.p, D.f, respectively. Stemeseder et al reported that dust mite-specific IgE levels were correlated with grass pollen and cat allergen-specific IgE [36]. In our study, the most common comorbid allergens in the polysensitivity group were dog dander, cat dander, ragweed , periplaneta americana and mould mix. Therefore, cross-reactivity between allergens may be one of the mechanisms by which HDM-SCIT is effective in treating patients with multiple allergies.

Research shown that SCIT with grass pollen has the same therapeutic effects among allergic rhinitis patients with monosensitivity and polysensitivity [37]. At the same time, several clinical studies of HDM-SLIT in allergic rhinitis showed that there was no statistical difference in clinical symptoms improvement and safety between

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mono- and polysensitized patients, and these conclusions were consistent with our findings in the treatment of AA children [38, 39].

In this study, we observed significant improvements in clinical symptom scores, FeNO, and lung function parameters in allergic asthma children with polysensitized after 3 years of treatment, with the same efficacy as the monosensitized group. And the polysensitized group had similar tolerability to the monosensitivity group. This result was clinically important because most children with AA were polysensitized. Based on our findings, HDM-SCIT can be recommended to more children with AA due to HDM in countries where its use is currently limited to children with monosensitized.

Our study has some limitations. Firstly, the limitation was the small number of enrolled children. Due to poor compliance, the number of children with asthma who can adhered to 3 years of treatment in the past decade was still relatively small, and only 51 children with allergic asthma completed the treatment, which meant it was difficult to get a large sample size in our study. Secondly, the immunological detection was not examined in all children after treatment, because some parents were not allowed, so it is hard to know whether there were any immunological changes between the two groups at the end of treatment. Thirdly, there was no follow-up on the long-term efficacy of the children after the treatment ended. In the future, we will conduct long-term follow-ups of all children who received HDM-SCIT to understand whether

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there is any difference in the long-term efficacy between the mono- and polysensitized groups of children with allergic asthma.

Conclusion

In this study, we demonstrated that HDM-SCIT had similar clinical efficacy in children with polysensitized allergic asthma compared to those seen in monosensitized, and the adverse reactions in the monosensitized and polysensitized groups are no statistical difference. Thus, HDM-SCIT should be considered in allergic asthma children who are polysensitized.

Statement of Ethi

The research was performed in accordance with the World Medical Association Declaration of Helsinki and has been granted an exemption from requiring ethics approval by the committee of Xijing Hospital of Fourth Military Medical University, Xi'an,China. Written informed consent was obtained from all parents. We thank the participants of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the National Natural Science Foundation of China (31371151 and 82170026); Technological Innovation Guidance Special Project of

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Shaanxi Province (2022QFY01-09); natural science basic research plan in shaanxi province (2022JQ-764) and Discipline Promotion Project of Xijing Hospital (XJZT18MJ23 and XJZT21L11).

Authorship contributions

All authors contributed to the study conception and design. Panpan Zhang and Yuanyuan Jia had the idea for the article and performed the data collection and analysis. The first draft of the manuscript was written by Panpan Zhang and Yuanyuan Jia. Xin Sun and Huajie Wu critically revised the work. Jinli Huang and Zenghui Jing commented on several drafts. All authors read and approved the final manuscript.

Data Availability Statement

All date generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author

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