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Efficacy and safety of sublingual dust mite drops in children with mono- or polysensitized allergic rhinitis

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ABSTRACT

Objective: To explore the efficacy and safety of sublingual house dust mite (HDM) drops in children with mono- or polysensitized allergic rhinitis.

Methods: We conducted a retrospective cohort study of 65 children with monosensitized AR and 118 children with polysensitized AR who were scheduled for sublingual administration of HDM drops from January 2015 to June 2016. Interleukin (IL)-2, IL-4, and IL-17α, transforming growth factor-β1 (TGF-β1), specific immunoglobulin E (IgE), and specific IgG4 were detected by ELISA. The efficacies were assessed using symptoms score and medication score. All the outcomes were measured 1 month before the study and 1 month after the end of the 2-year treatment.

Results: The total nasal symptoms score (TNSS) decreased significantly from 11.27 (9.81 ± 12.73) at baseline to 3.48(1.98 ± 4.98) at the end of sublingual treatment for the monosensitized AP group ($t = 30.00$, $P < 0.01$), and from 11.54(10.04 ± 13.04) to 3.56 (2.00 ± 5.16) for the polysensitized AR group ($t = 40.05$, $P < 0.01$), respectively. IL-2 and TGF-β1 increased significantly after treatment in contrast with before treatment in both the monosensitized group and the polysensitized group (both $P < 0.01$). In contrast, IL-4 and IL-17α decreased significantly after treatment compared with the baseline in both groups (both $P < 0.01$). Sublingual HDM drops were generally safe and well tolerant in both groups.

Conclusions: This study confirmed the efficacy and safety of sublingual AIT in both monosensitized and polysensitized AR patients (Chinese children).

1. Introduction

Allergic rhinitis (AR) has been one of the most common global health issues, which affects over 500 million people worldwide [1,2]. AR is commonly characterized by rhinorrhea, nasal obstruction, nasal itching, and sneezing. These symptoms can result in a poor quality of life, physical and mental problems, as well as a sleep disorder [3,4]. Moreover, patients with AR can also have an increased risk of asthma, especially when they are exposed to AR for long period time [5,6]; 30% of AR patients also suffer from asthma [7].

Although the pathophysiology of AR has not been thoroughly investigated, it was well documented that house dust mite (HDM) are strongly associated with AR [8]. Dermatophagoides pteronyssinus (*D. pteronyssinus*) and Dermatophagoides farina (D. farinae) are two of the most common HDMs, which have an IgE-mediated cross-reactive antibody response and accounted for > 90% of HDM-induced allergies worldwide [9,10]. HDM-induced allergies usually start very early in life, persist throughout adolescence and adulthood, and develop into other severe diseases during adulthood.

Specific allergen avoidance, symptomatic pharmacotherapy and allergy immunotherapy (AIT) are the main treatment choices for patients with AR. However, the effectiveness of allergen avoidance is limited in terms of feasibility. Moreover, symptom relief does not extend beyond the end of treatment [11]. AIT provides targeted disease-modifying effects in AR and is deemed as a guideline-recommended treatment [12,13]. In actual clinical practice, most AR patients were caused by polysensitized allergens. There are several specific AIT drugs for various allergens. While only an AIT drop for mono-sensitized AR is available in China. For the cross-reactive antibody response between different allergens, the AIT drop for mono-sensitized AR could also be effective for polysensitized AR patients. However, few studies have been conducted to investigate the efficacy and safety of AIT in head-to-head comparisons of mono-sensitized and polysensitized AR patients [14]. We conducted this retrospective study, aiming to explore the

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efficacy and safety of sublingual AIT in children with monosensitized and polysensitized AR.

2. Methods

2.1. Design and participants

We conducted a retrospective control study among patients with mono-sensitized or polysensitized AR in Xi'an Children's hospital, China. Participants included children with mono-sensitized or polysensitized AR, enrolled from May 2014 to June 2016. The Inclusion criteria for participants were as follows: (1) age ≤15 years; (2) fulfilled the classification of the Allergic Rhinitis and its Impact on Asthma guidelines [15]; (3) mono-sensitized AR were diagnosed with a positive result of specific immunoglobulin E (sIgE) to *D. pteronyssinus* or D. farinae allergens (HDM sIgE ≥0.35 IU/L), or a positive skin prick test (SPT) to *D. pteronyssinus* or D. farinae allergens (+++ or above); (4) polysensitized AR were diagnosed with at least another allergen by sIgE test or SPT besides *D. pteronyssinus* or(and) D. farinae allergens; (5) after avoiding exposure to allergen, the patient's allergic symptoms persisted, and physicians considered the symptoms were still associated with HDM; (6) the patient's allergic symptoms worse in spring and autumn or being exposed to dog fur. The main exclusion criteria were (1) patients with a history of asthma; (2) severe deviation of nasal septum by nasal endoscope; (3) ratio of adenoid to nasopharyngeal cavity width (A/N) > 0.71; (4) patients with diseases in gastroenterology, liver, renal, cardiovascular, brain, lung, and hematologic system.

2.2. Treatment schedule

Both mono-sensitized and polysensitized patients received sublingual administration of HDM drops (trade name Chang Di, produced by Zhejiang WOWU Biology Co., Ltd., Shanghai, China). The drops are administrated under the tongue in an empty mouth in the morning, and then were swallowed after 1–2 min. Patients were asked to avoid drinking water or eating food for at least 15 min after swallowing. The treatment included a dose-escalation phase and a later maintenance phase, recommended by the manufacturer. The dose-escalation phase included three weeks with protein concentrations of solutions 1 μg/mL for the first week, 10 μg/ml for the second week and 100 μg/ml for the third week, respectively. The doses were gradually increased daily (doses of 1st to 7th day were 1, 2, 3, 4, 6, 8 and 10 drops respectively) within each week (Table 1). The maintenance phase began from the fourth week with 3 drops and each drop containing protein concentrations of solutions 333 μg/ml. The total treatment lasted 2 years.

2.3. Serum inflammatory factor assay

One month before the study and 1 month after the end of the 2-year treatment, 3 mL of peripheral blood, from each participant, was collected to test for Interleukin (IL)-2, IL-4, and IL-17α, transforming growth factor-β1 (TGF-β1), sIgE, and sIgG4 testing. All the serum makers were detected by ELISA with commercially available kits (Shanghai WesTang Bio-Tech Co., LTD, Shanghai, China). The lower limits of detection were 4 pg/ml for IL-2, 1.95 pg/ml for IL-4, 7.8 pg/ml for IL-17α and 15.6 pg/ml for TGF-β1, respectively. All tests w ere manipulated according to the manufacturer's instructions.

2.4. Outcome measurements

The outcomes included symptoms score and medication score. All the outcomes were measured based on the patients clinical status 1 month before the study and 1 month after the end of the 2-year treatment. Nasal symptoms score consisted of 4 rhinitis symptoms (sneezing, rhinorrhea, pruritus and congestion), each of which had a four-point scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms [16]. The total nasal symptoms score (TNSS) was the sum of each symptom score. The medication score was based on the recommendations from World Allergy Organization (WAO) [17]: 1 point for antihistamines, 2 points for nasal corticosteroids and 3 for oral corticosteroids. The total medication score (TMS) related to the sum of each respective medicine score.

During the whole study, guardians of the patients were provided with diary cards to record the occurrence and severity of local and systemic reactions. The researchers collected safety information by telephone or from outpatient visits every month during the first 6 months and every 3 months from the 7th month to the end of treatment.

2.5. Statistical analyses

Database management and data analyses were performed using the Microsoft Excel 2010 software and Stata 11.0 software, respectively. Continuous variables with normal distribution were reported as mean ± standard deviation (SD). Means of two continuous normally distributed variables were compared using independent samples Student's test. For all the comparisons, differences were considered statistically significant at $P < 0.05$ (2 sided).

3. Result

3.1. Study participants

A total of 65 children with mono-sensitized AR and 118 children with polysensitized AR were included in this study (Fig. 1). The proportions of allergens causing mono-sensitized or polysensitized allergic rhinitis are shown in Table 2. In both groups, the mean age of subjects was around 7 years, and the mean duration of AR was approximately 2 years. Participants with severe AR accounted for most of the two groups. Baseline characteristics were balanced between the two groups (Table 3).

3.2. Efficacy outcomes

The TNSS decreased significantly from 11.27 (9.81 ± 12.73) at the baseline to 3.48(1.98 ± 4.98) at the end of sublingual treatment for the monosensitized AR group ($t = 30.00$, $P < 0.01$), and from 11.54 (10.04 ± 13.04) to 3.56 (2.00 ± 5.16) for the polysensitized AR group ($t = 40.05$, $P < 0.01$), respectively. Similarly, the TMS also decreased significantly from 1.67 (1.24 ± 2.10) at baseline to 0.52 (0.12 ± 0.92) at the end of sublingual treatment for the monosensitized AR group ($t = 15.79$, $P < 0.01$), and from 1.64

Table 1
Dose-escalation of HDM drops in mono-sensitized and polysensitized patients.

Time	Specification (μg/ml per drop)	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
1st week	1	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
2nd week	10	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
3rd week	100	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops

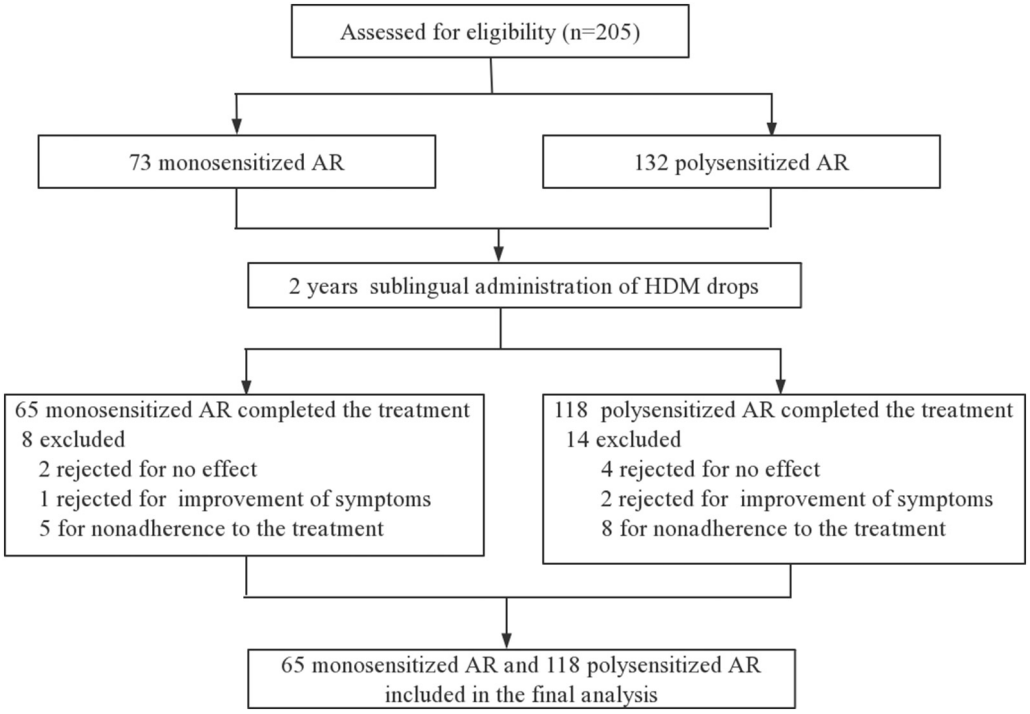

Fig. 1. Flow chart of this study.

(1.20 ± 2.08) to 0.55 (0.14 ± 0.96) for the polysensitized AR group ($t = 19.69$, $P < 0.01$), respectively (Fig. 2).

3.3. Immunological markers

IL-2 and TGF-β1 increased significantly after treatment compared with before treatment in both the monosensitized group and the polysensitized group (both $P < 0.01$). In contrast, IL-4 and IL-17α decreased significantly after treatment compared with the baseline in both groups (both $P < 0.01$) (Fig. 3).

The geometric means of the serum sIgE and sIgG4 before and after treatment are shown in Table 4. The levels of sIgE and sIgG4 increased significantly after treatment compared with before treatment in the monosensitized and polysensitized group (all $P < 0.05$).

3.4. Safety assessment

Sublingual HDM drops were generally safe and well tolerated in both groups. The overall prevalence of adverse events was 32.3% (21/65) in the monosensitized group and 39.0% (46/118) in the polysensitized group ($P = 0.37$), respectively. The most common adverse event was throat irritation, followed by oral pruritus and mouth edema. No significant differences were observed generally or specifically for each adverse event (Table 5).

4. Discussion

Most of the previous studies explored the efficacy and safety of sublingual immunotherapy (SLIT) among children and adults with monosensitized AR. Beyond that, this study also investigated the efficacy and safety of SLIT among children with polysensitized AR. We observed significant improvement in TNSS and TMS among children

Table 2
The proportions of allergens causing mono-sensitized or polysensitized allergic rhinitis.

Allergen	Mono-sensitized ($n = 65$)		Polysensitized ($n = 118$)	
	No	Proportion (%)	No	Proportion (%)
D. pteronyssinus	29	44.62	–	–
D. farinae	23	35.38	–	–
D. farinae + D. pteronyssinus	13	20.00	–	–
D. pteronyssinus + Artemisia powder	–	–	18	15.25
D. farinae + Artemisia powder	–	–	14	11.86
D. farinae + D. pteronyssinus + Artemisia powder	–	–	11	9.32
D. pteronyssinus + Phoenix tree pollen	–	–	16	13.56
D. farinae + Phoenix tree pollen	–	–	13	11.02
D. farinae + D. pteronyssinus + Phoenix tree pollen	–	–	14	11.86
D. pteronyssinus + Birch pollen	–	–	8	6.78
D. farinae + Birch pollen	–	–	6	5.08
D. farinae + D. pteronyssinus + Birch pollen	–	–	5	4.24
D. pteronyssinus + Artemisia powder + Phoenix tree pollen	–	–	3	2.54
D. farinae + Artemisia powder + Phoenix tree pollen	–	–	3	2.54
D. farinae + D. pteronyssinus + Artemisia powder + Phoenix tree pollen	–	–	2	1.69
D. farinae and/or D. pteronyssinus and (dog fur or cockroach or mold or shrimp)	–	–	5	4.24

Table 3
Baseline characteristics of patients.

	Monosensitized (n = 65)	Polysensitized (n = 118)	*P*
Age (years, mean ± SD)	7.5 ± 1.3	7.1 ± 1.4	0.06
Male/female, no.	22/43	52/66	0.18
Ethnicity, n (%)			
Chinese Han nationality	63(96.9)	112(94.9)	0.71
Others	2(3.1)	6(5.1)	
Duration of AR (years, mean ± SD)	1.8 ± 0.3	1.9 ± 0.5	0.14
Rescue medication use during pretreatment period, n (%)			
Yes	5(7.7)	12(10.2)	0.58
No	60(92.3)	106(89.8)	
Type of AR, n (%)			
Moderate	7(10.8)	11(9.3)	0.75
Severe	58(89.2)	107(90.7)	
Serum sIgE (IU/ml), n(%)			
0.35–3.4	8 (12.3)	16 (13.6)	0.96
3.5–34	20 (30.8)	33 (28.0)	
34–99	29 (44.6)	56 (47.5)	
100–	8 (12.3)	13 (11.0)	
TNSS (scores, mean ± SD)	11.27 ± 1.50	11.54 ± 1.42	0.23
Sneezing	2.67 ± 0.69	2.63 + 0.52	0.66
Nasal discharge	2.80 ± 0.41	2.97 ± 0.68	0.07
Nasal obstruction	2.88 ± 0.53	2.99 ± 0.47	0.15
Itching	2.93 ± 0.64	2.97 ± 0.56	0.66
TMS	1.67 ± 0.43	1.64 ± 0.44	0.70

AR, allergic rhinitis; SD, standard deviation; TMS, total medication score; TNSS, total nasal symptoms score.

with polysensitized AR, similar to that among children with monosensitized AR.

Symptoms caused by AR are the main reasons that affect patients quality of life. Thus, the primary treatment goal for AR is the ongoing relief of symptoms based on symptoms assessment. TNSS and TMS are the two main assessment indictors that evaluate the efficacy of allergy-specific immunotherapy. In this study, we found that TNSS and TMS had a significant decrease after treatment for children with monosensitized AR, which was in agreement with other studies [18,19]. Additionally, we also observed the satisfied efficacy in children with polysensitized AR, which was identified in a Phase 2/3 study conducted in Japan [20]. Although the mechanism of HDM allergy-specific immunotherapy to other specific allergen is not well known, these results suggest that HDM allergy-specific immunotherapy could create general efficacy for several allergens; not limited to dust mite allergy. However, a recent study showed that two years of sublingual grass pollen immunotherapy could not induce a persistent nasal response for patients with seasonal allergic rhinitis at a 3 year follow-up [21]. Further studies are needed to observe the long-term efficacy of SLIT in children with AR.

Several cells and cytokines play important roles in AR. It is well established that the T helper (Th) 1 cell and Th2 cell are involved in both the development of allergic sensitization and the pathology of allergic inflammation. The cytokines produced by Th1 cells are proinflammatory [22], while cytokines produced by Th2 cells suppress the potentially damaging effects of the Th1 immune reaction [23]. Regulatory T cells (Tregs) also influence both Th1 and Th2 cell-mediated inflammation. The lack of Tregs correlate to the emergence of allergic inflammation in addition to an increase in Th2 cells [24]. Furthermore, recent studies found that IL-17 contributes to eosinophil accumulation, induction of allergen-specific Th2 cell activation, and serum sIgE production, which suggests a regulatory role of IL-17 in established Th2-driven allergic immune responses [25]. Our study found that AIT could decrease the release of IL-4 and IL-17α, and increase the secretion of IL-2 and TGF-β1 to remedy the imbalance between different allergen-specific Th cells, which was also proven by other studies [26–28]. In addition, several other cells, cytokines and chemokines were also involve in activating and mediating allergic inflammation. Further studies are needed to investigated the roles of these factors on the pathogenesis of AR.

Specific IgE plays an important role in the inflammation of AR. Two studies observed that sIgE increases in the early period of AIT and then decreases [29,30]. Our study found only a moderate increase in sIgE at the end of AIT compared with baseline. This was consistent with the result of Carmen Rondón, et al. [30]. An analysis from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 also revealed that sIgE did not remain strongly associated with the reported symptoms [31]. Taken together, these results suggested that sIgE was not an optimal indicator to evaluate the effectiveness of AIT. In contrast, sIgG4 had a significant increase both in the monosensitized group and the polysensitized group. Although monosensitized and polysensitized patients may have appeared to differ in terms of their immune reactivity, previous studies found that several allergies had cross immunity [32]. Large-scale clinical trials showed that polysensitized patients also benefited at least as much from allergen immunotherapy as monosensitized patients with single AIT [33]. Thus, sIgG4 may be a promising immunological indicator to reflect the effectiveness of AIT for both monosensitized and polysensitized AR.

One patient developed wheezing during desensitization treatment. The symptom of wheezing alleviated after symptomatic treatment. However, wheezing reappeared after restarting desensitization treatment. Finally, the patient discontinued due to the wheezing. Further studies are needed to identify that whether wheezing is one of adverse events for desensitization treatment. Although AR patients report no history of asthma, we also suggest that pulmonary function test or bronchodilator reversibility testing is necessary for both monosensitized and polysensitized AR before desensitization treatment.

There were some limitations in our study. First, our study was a

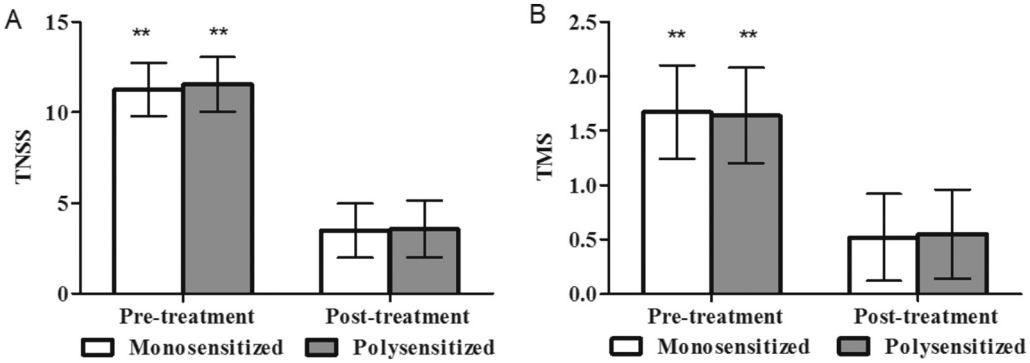

Fig. 2. TNSS and TMS in children with mono- and polysensitized allergic rhinitis pre- and post-treatment. Bars indicate the 95% confidence interval of means. $^{**}P < 0.01$.

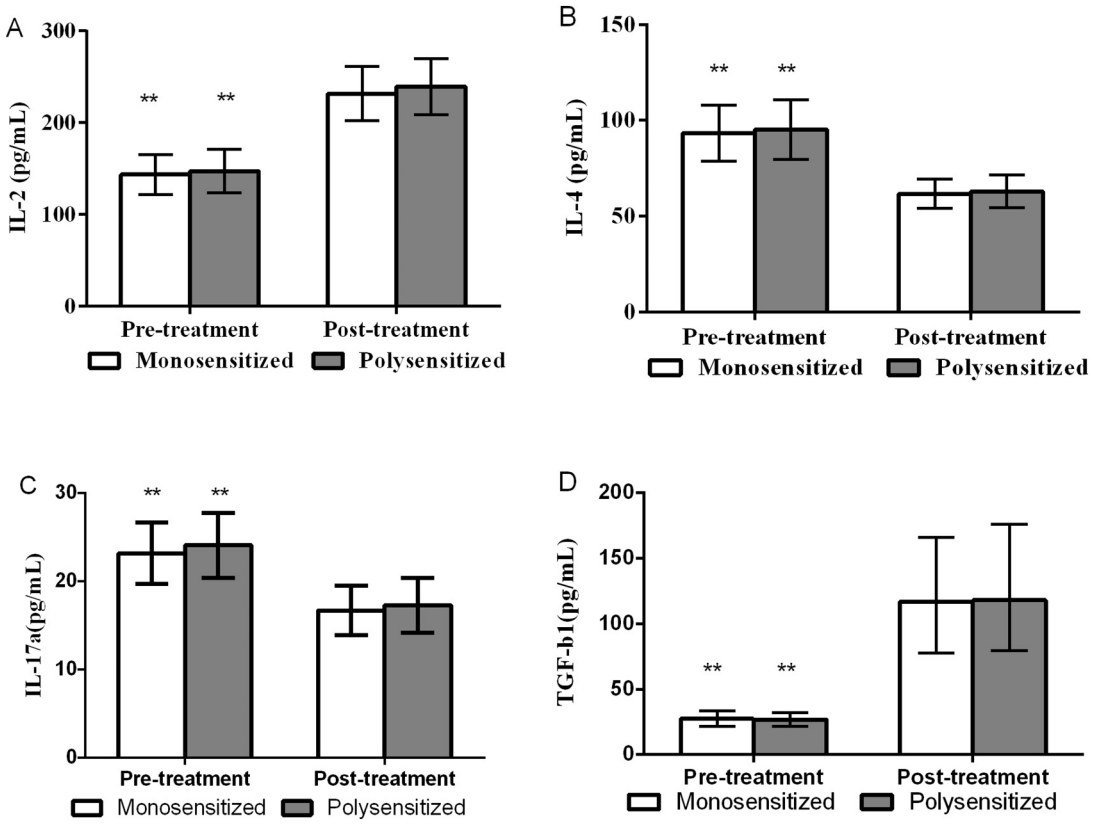

Fig. 3. IL-2, IL-4, IL-17α and TGF-β1 in children with mono- and polysensitized allergic rhinitis pre- and post-treatment. Bars indicate the 95% confidence interval of means. $^{**}P < 0.01$.

nonrandom study and did not include a non-treated control group. Hence, some conclusions should be tested by further studies. Second, most of patients developed polysensitized AR in Spring or Autumn. The baseline clinical features and outcomes at the end of treatment were measured in the same season for most patients, however, the temporal confounding factor could also affect our results. Third, we did not conduct long-term follow-ups for both the monosensitized and polysensitized groups after 2 years of treatment. Further studies are needed to identify the long-term efficacy of AIT for both monosensitized and polysensitized AR. Fourth, adverse events were collected by passive reporting in, which might underestimate the adverse events rates owing to the participants' potentially low initiative.

In conclusion, this study confirmed the efficacy and safety of sublingual AIT in both monosensitized and polysensitized AR patients, in Chinese children. Further studies are needed to identify the long-term efficacy of AIT for patients with monosensitized or polysensitized AR.

Table 5
Reported adverse events during the study.

	Monosensitized (n = 65)	Polysensitized (n = 118)	*P*
Total	21 (32.3)	46 (39.0)	0.37
Throat irritation	8 (12.2)	17 (14.4)	0.69
Oral pruritus	6 (9.2)	13 (11.0)	0.71
Mouth edema	5 (7.7)	12 (10.2)	0.58
Local rashes	3 (4.6)	5 (4.2)	0.70[a]
Eye itching	1 (1.5)	2 (1.7)	1.00[a]
Gastrointestinal intolerance	1 (1.5)	3 (2.5)	1.00[a]
Wheezing	0 (0.0)	1 (0.8)	1.00[a]

[a] *P* values obtained using Fisher exact test.

Statement of ethics

The study was approved by the institutional review board of Xi'an Children's hospital. Written informed consent was obtained from each participant' guardians before included.

Role of the funding source

This study was supported by Shaanxi Province Natural Science Foundation (No. 2019JQ-434), Shaanxi Health Research Fund (No.

Table 4
Comparison of sIgE and sIgG4 between pre-treatment and post-treatment in monosensitized and polysensitized group (mean ± SD).

	Monosensitized (n = 65)		Polysensitized (n = 118)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
sIgE(kU/L)	68.3 ± 3.8**	71.9 ± 4.1	72.9 ± 4.5*	74.7 ± 6.9
sIgG4(mg/L)	681.5 ± 19.4**	1175.4 ± 34.9	713.6 ± 22.7**	1208.1 ± 31.3

sIgE, specific immunoglobulin E; sIgG4, specific immunoglobulin G4.
* $P < 0.05$ compared between pre-treatment and post-treatment.
** $P < 0.01$ compared between pre-treatment and post-treatment.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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