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The changes in different symptom scores during subcutaneous immunotherapy in Chinese house dust mite allergic patients: a two-year, observational study

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Main Article

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Abstract

Background. Subcutaneous immunotherapy is an effective and safe treatment for allergic rhinitis and allergic asthma. Different symptom scores are used to evaluate the efficacy of subcutaneous immunotherapy in clinical trials.

Method. A total of 58 allergic rhinitis patients sensitised to house dust mites, with or without mild asthma, were included. Symptom score, medication score, visual analogue scale score and quality of life were assessed before and after 6, 12 and 24 months of subcutaneous immunotherapy.

Results. After two years of subcutaneous immunotherapy, asthma symptom scores nearly reached zero, whereas the scores remained higher for nasal symptoms. The changes in asthma symptom scores were markedly different ($p < 0.05$) and occurred faster than the changes in nasal symptom scores when compared between monosensitised and polysensitised groups. Significant reductions in visual analogue scale score and medication score were demonstrated after subcutaneous immunotherapy.

Conclusion. Two-year subcutaneous immunotherapy with house dust mite vaccine is an effective treatment for both monosensitised and polysensitised allergic patients. The changes in asthma symptom scores were markedly different and occurred quicker than the changes in nasal symptom scores in Chinese house dust mite allergic patients.

Introduction

The prevalence of allergic diseases has increased rapidly in the past few decades.[1] As an example, allergic rhinitis is a major health issue that affects nearly 600 million people worldwide.[2,3] The economic burden of allergic rhinitis is also substantial.[4] There are many tests that can be used to confirm an allergy diagnosis and several drugs to treat allergy symptoms; however, allergen-specific immunotherapy remains the only aetiological treatment.

As an aetiological treatment method, subcutaneous immunotherapy can provide sustained relief from symptoms and improve life quality. At the same time, subcutaneous immunotherapy has the potential to prevent disease progression.[5] A previous study found that early intervention with immunotherapy helps to improve the efficacy of allergic rhinitis treatment.[6] Nowadays, subcutaneous immunotherapy is considered to be the first-line therapy for allergic diseases, and its indications, contraindications, limits and practical aspects are well defined in numerous guidelines.[7,8]

Allergic diseases are not only associated with environmental factors; genetic susceptibilities are also known to be allergy risk factors.[9] The link between allergic rhinitis and asthma is evident: approximately 20 per cent of allergic rhinitis patients develop asthma later in life, and more than 70 per cent of asthma patients report nasal symptoms.[10] Subcutaneous immunotherapy reduces the risk of asthma developing in patients with allergic rhinitis,[11] and its application to allergic rhinitis and asthma patients is the focus in clinical practice.

In China, house dust mites are the dominant allergen in patients with allergic rhinitis and asthma, and the efficacy of subcutaneous immunotherapy has not yet been fully investigated. In this study, two-year subcutaneous immunotherapy was carried out using house dust mite extract in allergic rhinitis patients with or without mild asthma. The changes in different symptom scores during the two-year subcutaneous immunotherapy period were observed and compared.

Materials and methods

Subjects

A total of 58 patients were recruited for this study. All patients finished the two years of standardised subcutaneous immunotherapy at the Department of Otorhinolaryngology,

Central Hospital of Zibo, China, from 2014 to 2016. The patients had a diagnosis of allergic rhinitis in accordance with the European Academy of Allergology and Clinical Immunology guidelines.[12] Approval for this study was obtained from the Institutional Review Board of the Central Hospital of Zibo. Informed written consent was obtained from all adult patients and guardians of paediatric patients before inclusion in the study.

Inclusion criteria were: a clinical history of mite-induced allergy requiring treatment; typical symptoms and signs of allergic rhinitis; a positive skin-prick test response to *Dermatophagoides pteronyssinus* (wheal diameter of at least 3 mm; ALK, Hørsholm, Denmark); and a positive specific immunoglobulin E (IgE) level against *D pteronyssinus* in serum (at least 0.7 kU/l; CAP Pharmacia, Uppsala, Sweden).

Exclusion criteria were: severe or uncontrolled asthma; being treated with beta-blockers or angiotensin-converting enzyme inhibitors; significant cardiovascular abnormalities; immune system disorders; a malignant tumour; pregnancy; nasal polyps; chronic sinusitis; and previous immunotherapy within the past three years.

Subcutaneous immunotherapy

Patients were treated in the clinic with standardised house dust mite extract. Administration of the *D pteronyssinus* extract (Alutard SQ; ALK) by injection was performed using a dose increase phase and a maintenance phase schedule. An initial dosage of 20 SQ-U was given and increased every week for 15 weeks, as follows: 20, 40, 80, 200, 400, 800, 2000, 4000, 8000, 10 000, 20 000, 40 000, 60 000, 80 000 and 100 000 SQ-U. At the 16th week, the maximum dose of 100 000 SQ-U was given. After that, the maximum dose was maintained during the maintenance phase, and the injection interval time was gradually extended to six weeks. Patients were observed at the clinic for 30 minutes after each injection to prevent the occurrence of adverse reactions.

Clinical efficacy

Visual analogue scale scores

Visual analogue scale (VAS) scores were recorded before and after 6, 12 and 24 months of treatment to evaluate the combination of allergic symptoms. Patients marked their score on a horizontal line ranging from 0 to 10, with 0 points representing no allergic symptoms and 10 points representing extremely severe allergic symptoms.

Medication scores

All patients were allowed to use rescue medications when necessary. The recommended rescue medications are antihistamines, inhaled beta2 bronchodilators, intranasal or inhaled corticosteroids, and oral corticosteroids. The following values were given for each day of use: oral or intranasal antihistamines, 1 point; inhaled beta2 bronchodilators, 1 point; intranasal corticosteroids, 2 points; inhaled corticosteroids, 2 points; and oral corticosteroids, 3 points. The sum of these values was calculated as the medication score.

Symptom scores

The total nasal symptom score[13] and the total asthma symptom score[13] were assessed using a questionnaire. The total nasal symptom score includes symptoms of nasal obstruction, nasal itching, sneezing and nasal discharge, which were evaluated using a four-point scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). The sum of the four individual nasal symptom scores was recorded as the total nasal symptom score.

Patients with concomitant asthma were also given an asthma symptom score. Asthma symptoms included: coughing, dyspnoea, wheezing, chest congestion and so on. Daytime asthma symptoms were scored from 0 points (no symptoms) to 5 points (the severest symptoms) according to the severity and frequency of asthma symptoms. Night-time asthma symptoms scores ranged from 0 points (no awakening by asthma) to 4 points (awake all night). The sum of daytime and night-time asthma symptom scores gave the total asthma symptom score.

Quality of life

Quality of life was investigated using the Rhinoconjunctivitis Quality of Life Questionnaire[14] and the Asthma Quality of Life Questionnaire.[15] These questionnaires were completed before and after receiving immunotherapy for 6, 12 and 24 months.

The Rhinoconjunctivitis Quality of Life Questionnaire was designed to assess the health status of patients with allergic rhinitis or rhinoconjunctivitis, focusing on seven domains (nasal symptoms, eye symptoms, non-hay fever symptoms, practical problems, emotional function, activities limitation and sleep). Each domain was evaluated using a rating scale of 0–6 points, with 0 points and 6 points indicating the best and worst quality of life, respectively. The higher the Rhinoconjunctivitis Quality of Life Questionnaire scores, the worse the quality of life was.

The Asthma Quality of Life Questionnaire focused on four domains (activity limitations, symptoms, emotional function and exposure to environmental stimuli) that might be significantly affected by asthma. Each domain was evaluated on a rating scale of 1–7 points, with 1 point and 7 points indicating the worst and best quality of life, respectively. The higher the Asthma Quality of Life Questionnaire scores, the better the quality of life was.

Safety evaluation

Adverse events were recorded and classified as local or systemic reactions. Local reactions mainly comprised erythema, itching and swelling of injection sites, which did not need special treatment and could resolve spontaneously, usually within 24 hours.[16] Systemic reactions were symptoms located far away from injection sites after vaccination, including rhinitis, asthma symptoms, urticaria, angio-oedema and anaphylactic shock. Systemic reactions were graded according to the European Academy of Allergology and Clinical Immunology standards.[13]

Statistical analysis

Statistical analysis was carried out using SPSS® software (version 22). Various indicators were compared before and after treatment with non-parametric statistical tests. Continuous variables were described using the median and 25th–75th interquartiles. Comparisons were performed using the Mann–Whitney U test. *P*-values lower than 0.05 were considered statistically significant.

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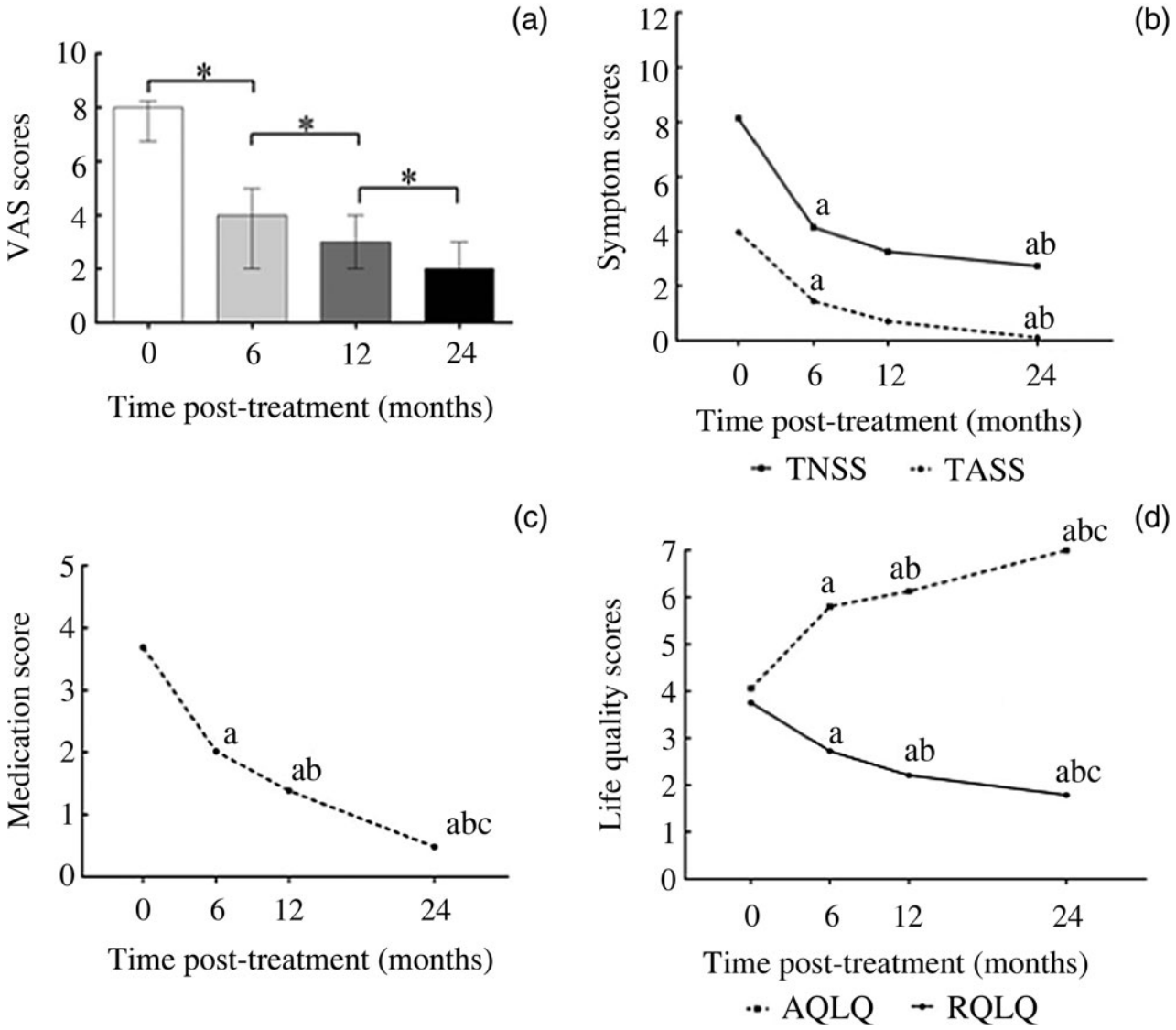

Fig. 1. Graphs showing pre- and post-treatment changes (at 6, 12 and 24 months) in: (a) visual analogue scale (VAS) scores (median and 25th–75th interquartiles); (b) total nasal symptom scores (TNSSs) and total asthma symptom scores (TASSs) (median); (c) medication scores (median); and (d) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Asthma Quality of Life Questionnaire (AQLQ) scores (median). *$p < 0.05$; 'a' indicates $p < 0.05$, difference from baseline; 'b' indicates $p < 0.05$, difference from 6 months; and 'c' indicates $p < 0.05$, difference from 12 months

Results

Patients

A total of 58 patients (16 female and 42 male) aged from 5 to 53 years (median age of 11 years) completed the 2-year subcutaneous immunotherapy according to the standardised process. All subjects were allergic to house dust mites, and 40 per cent of patients (23 of 58) were also sensitised to other allergens. The most common other allergen was pollen and then alternaria fungi. Ninety per cent of allergic rhinitis patients (52 of 58) also had asthma.

Safety

The 58 patients were given 1740 allergen injections in total. Local reactions were mainly resolved spontaneously and did not need special treatment. There were 25 systemic reactions triggered by injections in 16 patients; the incidence of systemic reaction was 1.4 per cent. Of the systemic reactions, 20 were classified as grade 1 (80 per cent) and 5 were classified as grade 2 (20 per cent). No serious adverse events or anaphylactic shock occurred. All systemic reactions were treated successfully with oral antihistamines or glucocorticoid aerosol inhalation.

Clinical efficacy assessment

The VAS score was used to evaluate the overall efficacy of subcutaneous immunotherapy. As shown in Figure 1a, VAS score was 8 (6.75, 8.25) out of 10 points before treatment, and declined to 2 points (1.00, 3.00) by the end of the two-year treatment. The reduction of VAS score was evident from: the baseline to 6 months, 6 to 12 months, and 12 to 24 months ($p < 0.05$).

The changes in total nasal symptom scores and total asthma symptom scores during immunotherapy are shown in Figure 1b. Total nasal symptom scores and total asthma symptom scores showed a sustained decline during the two-year treatment period. After 6, 12 and 24 months of subcutaneous immunotherapy, the patients showed significant improvements in rhinitis and asthma symptoms when compared with symptoms before treatment ($p < 0.05$). Compared

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Table 1. Individual nasal symptom scores pre- and post-treatment

Time	Nasal obstruction	Nasal itching	Sneezing	Nasal discharge
Baseline	2.00 (1.00, 3.00)	2.00 (1.00, 2.00)	2.00 (1.00, 3.00)	3.00 (2.00, 3.00)
6 months	1.00 (1.00, 2.00)*	1.00 (0.00, 2.00)*	1.00 (0.00, 1.00)*	1.00 (0.00, 2.00)*
12 months	1.00 (0.00, 1.00)*	1.00 (1.00, 1.00)*	0.50 (0.00, 1.00)*	1.00 (0.00, 2.00)*
24 months	1.00 (0.00, 1.00)*†	1.00 (0.00, 1.00)*	0.00 (0.00, 1.00)*	1.00 (0.00, 1.00)*

All values are given as the median and 25th–75th interquartiles. *$p < 0.05$, difference from baseline; †$p < 0.05$, difference from six months

Table 2. Asthma symptom scores pre- and post-treatment

Time	Daytime symptoms	Night-time symptoms
Baseline	3.00 (2.00, 3.00)	1.00 (1.00, 2.00)
6 months	0.00 (0.00, 1.25)*	0.00 (0.00, 1.00)*
12 months	0.00 (0.00, 1.00)*	0.00 (0.00, 1.00)*
24 months	0.00 (0.00, 0.00)*†	0.00 (0.00, 0.00)*†

All values are given as the median and 25th–75th interquartiles. *$p < 0.05$, difference from baseline; †$p < 0.05$, difference from six months

with scores at 6 months, there was no significant difference for total nasal symptom scores or total asthma symptom scores at 12 months ($p > 0.05$). However, a significant decrease of the total nasal and asthma symptom scores could be observed at 24 months ($p < 0.05$) when compared with 6 months. Similarly, there was continued decline in rescue medication use during the two-year study period (Figure 1c). Significant reductions of medication scores were achieved from: the baseline to 6 months, 6 to 12 months, and 12 to 24 months ($p < 0.05$).

The scores for quality of life associated with rhinitis and asthma after treatment are shown in Figure 1d. The Rhinoconjunctivitis Quality of Life Questionnaire score showed that significant improvements were achieved from: the baseline to 6 months, 6 to 12 months, and 12 to 24 months ($p < 0.05$). The overall Asthma Quality of Life Questionnaire score showed a continuous increase, representing sustainable improvements in quality of life related to asthma. The differences from the baseline to 6 months, 6 to 12 months, and 12 to 24 months were significant ($p < 0.05$). Furthermore, the overall Asthma Quality of Life Questionnaire score increased to nearly 7 points at the end of the treatment, meaning there was almost no quality-of-life impairment caused by asthma.

Individual nasal symptom scores are exhibited in Table 1. Before treatment, nasal discharge had the highest score, which was 3 points (2.00, 3.00). Sneezing achieved the best score after two-year subcutaneous immunotherapy with a score of 0 points (0.00, 1.00). After six months of subcutaneous immunotherapy, all four individual nasal symptoms improved significantly compared with those before treatment ($p < 0.05$). However, compared with 6 months of treatment, only nasal obstruction demonstrated significant reductions at 24 months ($p < 0.05$).

Individual daytime and night-time asthma symptom scores are shown in Table 2. Daytime symptoms were severer than night-time symptoms at the beginning, scoring 3 points (2.00, 3.00) and 1 point (1.00, 2.00), respectively. After six months of subcutaneous immunotherapy, great reductions in both daytime and night-time symptom scores could be achieved, and the differences were significant ($p < 0.05$). Moreover, compared with 6 months, both symptom scores

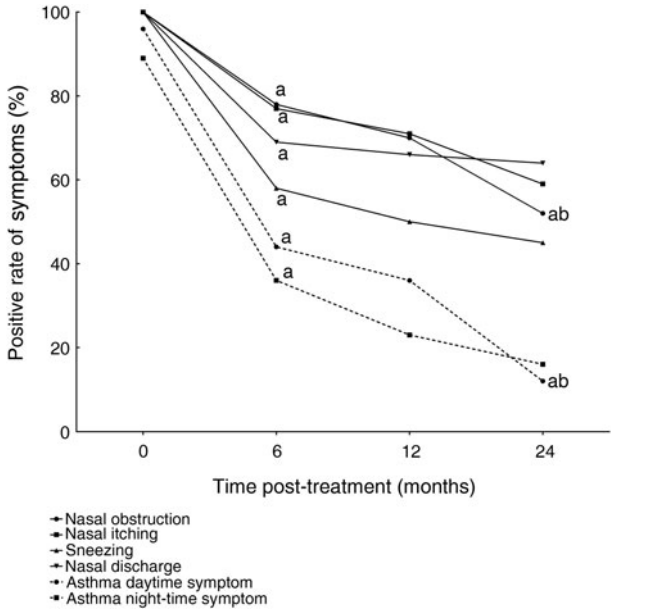

Fig. 2. Positive rate of individual nasal and asthma symptoms pre- and post-treatment (at 6, 12 and 24 months). 'a' indicates $p < 0.05$, difference from baseline; 'b' indicates $p < 0.05$, difference from 6 months

were markedly lower at 24 months ($p < 0.05$), when they declined to the same level of 0 points (0.00, 0.00).

The positive rate of individual nasal and asthma symptoms during immunotherapy are shown in Figure 2. The positive rate approached 100 per cent for almost every symptom before treatment. After six months of subcutaneous immunotherapy, all symptom positive rates significantly decreased ($p < 0.05$). However, compared with 6 months, none showed significant differences at 24 months, except for nasal obstruction and daytime asthma symptoms ($p < 0.05$). It is worth noting that the positive rate was more than 40 per cent by 24 months for the four nasal symptoms, whereas the positive rate for the daytime and night-time asthma symptoms was below 20 per cent by that time. The findings of symptom positive rates were generally in agreement with the results of nasal and asthma symptom scores.

Among the patients receiving the two-year subcutaneous immunotherapy, the monosensitised group included 35 patients who were sensitised to house dust mites only, and the polysensitised group included 23 patients who were sensitised to both house dust mites and other allergens. Total nasal symptom scores and total asthma symptom scores of the monosensitised patients were significantly lower than those of the polysensitised patients before treatment ($p < 0.05$). After 24 months of immunotherapy, there was no significant difference between the two groups in both symptom scores (Table 3). The decrease of the symptom scores in the

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Table 3. TNSS and TASS according to sensitisation status pre- and post-treatment

	Total nasal symptom score			Total asthma symptom score		
Time	Monosensitised	Polysensitised	*P*-value	Monosensitised	Polysensitised	*P*-value
Baseline	7.00 (6.00, 9.75)	10.00 (7.75, 11.00)	0.01	3.00 (2.00, 4.00)	4.00 (3.00, 6.00)	0.01
24 months	2.00 (0.00, 4.00)	2.00 (1.50, 4.00)	0.98	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.56

All values are given as the median and 25th–75th interquartiles. TNSS = total nasal symptom score; TASS = total asthma symptom score

polysensitised group is much larger than in the monosensitised group (Figure 3). The changes in asthma symptom scores exhibited marked differences after only 6 months of subcutaneous immunotherapy ($p < 0.05$), whereas the changes in nasal symptom scores took 12 months to show significant differences.

Discussion

The prevalence of allergic diseases has increased annually, and brought a heavy burden to both patients and society.[4] Sex differences in the prevalence of allergic rhinitis have been observed in previous studies.[17] As shown in our results, the male predominance of rhinitis prevalence also exists in Chinese patients.

The majority of allergic rhinitis patients in China are sensitised to house dust mites. Exposure to house dust mite allergens in early childhood is a risk factor for the subsequent development of asthma.[18] Currently, the treatment methods include allergen avoidance, pharmacological therapy, immunotherapy and patient education. However, completely avoiding house dust mite contact is difficult in real life, and allergy medication has to be used long-term to control symptoms.[19] Additionally, the therapeutic effectiveness and safety of subcutaneous immunotherapy with house dust mite vaccine for allergic rhinitis patients with asthma remain difficult issues in clinical treatment. Allergen-specific immunotherapy has been the only treatment that can prevent disease progression by regulating immunological function,[20–23] which plays a critical role in the whole treatment system.[24]

The safety of subcutaneous immunotherapy is an important focus of attention in clinical practice. According to the multicentre and large-sample clinical observation in China, the incidence of systemic reaction with house dust mite vaccine is 0.47 per cent.[25] The higher systemic adverse reaction ratio in this study may be caused by the large number of subjects who are children or asthma patients. It is not clear how the higher number of children would affect systemic side effects of subcutaneous immunotherapy, but our results suggest that being a child may be a risk factor for systemic side effects.

To clarify this point, further evaluation of the systemic adverse reaction ratio in different age groups is recommended. Though there are some side effects, subcutaneous immunotherapy is still deemed safe when conducted in the right way and used for individualised treatment. After six months of subcutaneous immunotherapy, there were significant improvements in allergic symptoms, and the VAS score continued to decline during the two-year treatment (Figure 1a). These results are consistent with the general opinion that standardised subcutaneous immunotherapy with house dust mite extract is an effective and safe therapy. Subcutaneous immunotherapy maintenance treatment for over two years can yield optimal clinical outcomes.[8,12]

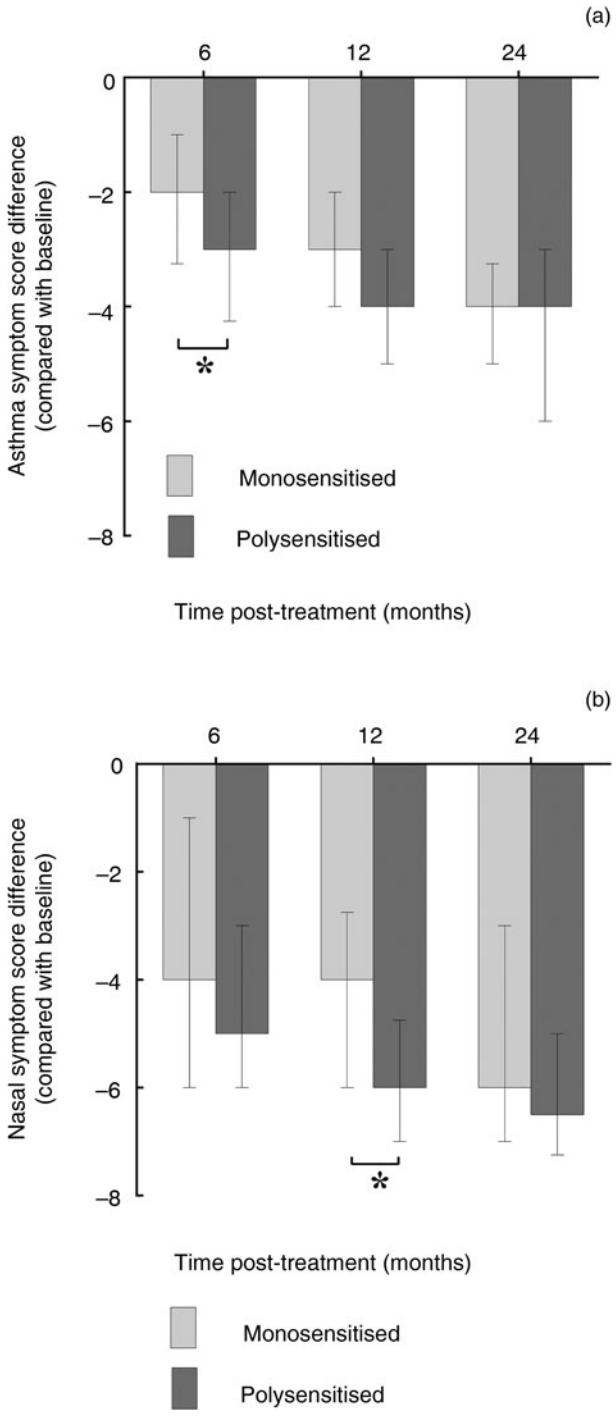

Fig. 3. Graphs showing the changes in (a) nasal and (b) asthma symptom scores compared with baseline (median and 25th–75th interquartiles) between monosensitised and polysensitised groups. *$p < 0.05$

In recent years, much effort has been made to find an objective indicator, such as IgE[26] or exhaled nitric oxide,[27] to evaluate the therapeutic effect of immunotherapy. But in 2013,[8] the

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World Allergy Organization still defined the need for medication use and symptom severity as primary measurements in the clinical outcome of subcutaneous immunotherapy. Successful immunotherapy often results in improvements in symptoms and a reduction in medication score. However, as a useful measure of the efficacy of subcutaneous immunotherapy in a clinical setting, the changes in different symptom scores during immunotherapy have received little focused investigation. In the present study, nasal and asthma symptom scores were compared and investigated in different ways.

Subcutaneous immunotherapy can ameliorate asthma symptoms significantly within 24 months, whereas the effect on allergic rhinitis is not as good. After 24 months of subcutaneous immunotherapy, asthma symptoms basically disappeared (Table 2, Figure 1b), and full marks were nearly reached in the Asthma Quality of Life Questionnaire (Figure 1d). However, for allergic rhinitis, three of the four nasal symptoms still existed (Table 1, Figure 1b), and the Rhinoconjunctivitis Quality of Life Questionnaire score was unsatisfactory at 24 months (Figure 1d). This may be explained by the younger age of the patients involved in the present study. Inflammation and remodelling of the airway were not too prominent in younger patients, allowing them to respond to treatment effectively. Another explanation is that house dust mite allergy is the main aetiological factor for these asthma patients.

- Despite some side effects, subcutaneous immunotherapy is deemed safe when conducted correctly using individualised treatment
- Six months' subcutaneous immunotherapy led to significant improvements in allergic symptoms and visual analogue scale scores
- Improvements continued during the two-year treatment period
- Subcutaneous immunotherapy can ameliorate asthma symptoms within 24 months; the effect is not as good for allergic rhinitis
- The symptom positive rate showed a similar decrease in rhinitis and asthma symptom scores, and is valid for evaluating subcutaneous immunotherapy efficacy
- Two-year subcutaneous immunotherapy with house dust mite vaccine is beneficial for monosensitised and polysensitised allergic patients

In the present study, the response to subcutaneous immunotherapy has also been assessed by the symptom positive rate (Figure 2). Compared with 6 months, the positive rate decreased significantly at 24 months ($p < 0.05$) for both nasal obstruction and daytime asthma symptom scores. The symptom positive rate showed the same trend with symptom scores in rhinitis and asthma patients, and it could be another valid method to evaluate subcutaneous immunotherapy efficacy.

House dust mite vaccine was used for both monosensitised and polysensitised allergic patients in this study; our results indicated that the house dust mite vaccine is a beneficial treatment for both groups. This might be because the house dust mite was the main cause of allergy. The cross-reactions between house dust mite and other allergens may also be relevant. The changes in asthma symptom scores were markedly different ($p < 0.05$) and occurred quicker than the changes in nasal symptom scores (Figure 3), which is consistent with the better control of asthma symptoms in the present study.

According to the European Academy of Allergology and Clinical Immunology and World Allergy Organization guidelines, the recommended duration of subcutaneous immunotherapy is three to five years in order for long-term effects of immunotherapy to be acquired. The possible maintenance of the positive effect demonstrated in the study after two years of subcutaneous immunotherapy was considered. All patients in this study are continuing subcutaneous immunotherapy for a third year, and they will continue to have follow-up visits.

In summary, this study observed and compared the changes in different symptom scores during two-year subcutaneous immunotherapy for the first time. We found that subcutaneous immunotherapy is an effective and safe therapy in Chinese house dust mite allergic patients. The changes in asthma symptom scores were markedly different and occurred faster than the changes in nasal symptom scores in these patients. But as the study subject number is small, it remains to be determined whether these findings are common.

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Competing interests. None declared

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