Review Article

House dust mite subcutaneous immunotherapy in Chinese patients with allergic asthma and rhinitis

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Abstract: The efficacy of allergen immunotherapy (AIT) has been reported with different allergens including house dust mites (HDM). HDM are the most prevalent allergens in patients with asthma and/or rhinitis in China. In addition to improving symptoms, reducing medication need, and improving quality of life, AIT can change the course of allergic disease and induce allergen-specific immune tolerance. To date, the use of AIT is becoming more acceptable in China, and there are many studies about the current clinical practice immunotherapy. In this paper we discuss the main aspects of AIT undertaken in China; including symptom and medication scores, pulmonary function and airway hyperresponsiveness, specific allergen sensitivity, safety evaluation, and mechanisms underlying AIT. This review will provide some important information on AIT treatment strategies to doctors, healthcare professionals and organizations involved in the AIT in China. According to the studies in China, successful AIT may induce antibody responses and cellular reactions in relation to the significant improvement in clinical symptoms, reducing the need for medications and maintenance of stable pulmonary functions.

Keywords: Allergen; house dust mite (HDM); allergen immunotherapy (AIT); allergic rhinitis (AR); allergic asthma

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Introduction

The best strategy for treating allergic diseases is a combination of approaches including avoiding allergens, patient education, appropriate drug therapy, and allergen immunotherapy (AIT). AIT is recommended by Global Strategy for Asthma Management and Prevention (GINA) for a treatment option if allergy play a prominent role, e.g., asthma with allergic rhinoconjunctivitis (1). Currently, two types of AIT are mainly applied in clinical practice: subcutaneous immunotherapy (SCIT) is conventionally administered by the subcutaneous route, and sublingual immunotherapy (SLIT) is a new immunotherapy by sublingual administration of soluble allergen extracts (2,3). The efficacy of SCIT and SLIT for both children and adults for pollen, pet dander, and house dust mite (HDM) has been confirmed in recent systematic meta-analyses (4,5). However, the exact mechanism underlying the therapeutic effect of AIT is still unclear, and the clinical practice of immunotherapy in China has yet to be standardized. The key issue in this review is to optimize the therapeutic effect of AIT, confirm that it truly changes the patient's allergic status, and maintain a long-term efficacy.

Exposure to HDM allergen is a major cause of perennial allergic rhinitis (AR) and/or asthma in China, predominantly *Dermatophagoides pteronyssinus* (Der p) and

Dermatophagoides farina (Der f) (6). Since 2001, SCIT in the form of an HDM vaccine has been widely used in China. This review summarizes the clinical efficacy of SCIT and its possible underline mechanisms on allergic asthma and/or rhinitis.

Symptom and medication scores

All reports have confirmed that SCIT significantly alleviated the symptoms of AR and/or allergic asthma and reduced the dosage of other medications. A total of 129 patients completed a multicenter, randomized, double-blinded, placebo-controlled 1-year study of mild to moderate allergic asthma conducted by Wang *et al.* (7). In this study, subjects between the ages of 6 and 45 years who fulfilled the GINA guidelines for stabilized mild to moderate asthma with their lung function of forced expiratory volume in 1 second ≥70% of predicted (8), and had positive skin prick test (SPT) and specific immunoglobulin E (sIgE) to Der p were included. Subjects were excluded with positive SPT to animals and pets at home. Percentage of the subjects accompanied with rhinitis in active and placebo were 90.6% and 84.6% respectively without significant difference. During the study, subjects were asked to rate each of the daytime symptoms of shortness of breath, wheeze, cough and chest tightness from 0 to 5. The mean of the four scores was recorded as the daytime symptom score. Night-time symptoms were scored from 0 to 4 according to the frequency of nocturnal and early morning awakening by asthma. The daily symptom score was the sum of the daytime and night-time symptom scores. The medication score is calculated by assigning a score of 1 to each puff of salbutamol/terbutaline or the equivalent dose of oral β_2-agonist. Just prior to unblinding, subjects were asked to give self-evaluations in their improvement in exacerbation frequency, exacerbation severity and overall symptoms, based on their own impression. The authors noted significant differences between the treated and control groups with respect to asthma symptom scores, starting from 7 months of treatment. In the treated group, the asthma symptom and medication scores of the patients were significantly lower in maintenance phase than those in up-dosing phase. After 1 year, the self-evaluations of improvements were significantly better in the treated group than in the control group. The authors also analyzed the effect of inhaled corticosteroids (ICS) on asthmatic symptoms and the usage of as needed inhaled and oral short-acting β_2-agonists. Their results showed that in patients who were already using ICS with constant dose during the treatment period, SCIT significantly improved their asthmatic symptoms and reduced their need for as needed β_2-agonists; in patients who did not start to use ICS before the study, although SCIT did not significantly improve their asthmatic symptoms, it reduced their need for rescued β_2-agonists. These results indicated that SCIT can relieve the symptoms and reduce the need for medications in asthmatic patients. The authors also followed 38 patients who received SCIT for 2–3 years in one of the centers, and they found that SCIT continued to improve asthma symptoms and reduce the medication doses.

Qi *et al.* (9) reported early intervention with SCIT helps to improve the efficacy of AR treatment and local reactions might predict successful SCIT. Zhang *et al.* (10) treated 154 patients with moderate to severe persistent AR using a cluster SCIT schedule and followed them for 1 year. They showed the rhinitis scores significantly decreased starting from the 4th week after treatment, which was earlier than using the conventional injection regimen. The cluster schedule also reduced the duration of up-dosing phase by over 60% as compared to the conventional schedule and improved treatment compliance. Rhinitis and medication scores of the patients significantly decreased after 1 year, and scores for quality of life of patients with rhinitis significantly increased, indicating a significant improvement of overall life quality. Feng *et al.* (11) compared the combined symptom and medication (including inhaled and nasal corticosteroid, inhaled short acting β_2 agonists, and oral antihistamine) scores (SMS) between SCIT patients and only-medication-treated patients, and found that SCIT patients had a significant improvement in SMS from weeks 52 to 156 compared with medication-treated control subjects. Lai *et al.* (12) also reported that the symptom and medication scores of asthma in children and adults reduced significantly after 25 weeks of SCIT while there were no significant differences between children and adults during the whole course (*Table 1*).

Pulmonary function and airway hyperresponsiveness

The responses of pulmonary functions to SCIT are different with different studies. Wang *et al.* (7) reported the pulmonary functions of the patients in treated group did not change after 1 year of treatment, and the variations in peak expiratory flow (PEF) and peak expiratory flow rate (PEFR) in the morning versus evening did not show significant

Table 1 The recent study outcomes of AIT clinical effects in China

Study	Study design	Characteristics of the participants and allergen for AIT	Main findings
Wang 2006 (7)	A double-blind, placebo-controlled study involving 132 asthmatic subjects 52-week of SCIT	Subjects between the ages of 6 and 45 years. The maintenance dose was 9.8 μg of Der p	Immunotherapy resulted in a significant decline in symptom (P<0.002) and medication (P<0.007) scores during the second half of the treatment period
Qi 2016 (9)	A total of 284 consecutive patients were recruited Receive 3 years of SCIT	The mean age was 17.6 years (range, 5–65 years). The maintenance dose was 4.5 μg of Der p	After 3 years of AIT, the scores for visual analog scale was lower in the responder group than in the non-responder group (2.9±1.7 *vs.* 5.6±1.4)
Zhang 2008 (10)	154 patients with allergic rhinitis to Der p were allocated Receive 1 year of cluster AIT	The mean age was 24 years (range, 6–62 years). The maintenance dose was 9.8 μg of Der p	Cluster AIT significantly reduced the symptom scores and total medication score of patients enrolled (P<0.01) The AIT group also had a significant improvement in the Rhinoconjunctivitis Quality of Life Questionnaire
Feng 2018 (11)	A total of 83 asthma or/and AR patients were recruited: receive 3 years of SCIT	35 children (age ≤14 years) and 48 adults (age 15–57 years). The maintenance dose was 9.8 μg of Der p	AIT patients had a significant improvement in SMS from week 52 to 156 compared with medication-treated control subjects SCIT patients had greatly decreased AHR grades at week 52 to 156
Wang 2006 (13)	68 asthmatic subjects Receive 25 week of SCIT FEV_1, PEF, scores of symptoms and medications were measured	The mean age was 8 years (range, 5–14 years)	The FEV_1, PEF significantly increased after AIT The symptoms and medications scores were significantly decreased after AIT
Lin 2007 (14)	37 patients of AR combining with mild-moderate asthma were recruited Receive 3 years of SCIT FEV_1, PEF, symptomatic scores and skin test index were measured	The mean age was 20 years (range, 6–49 years). The maintenance dose was 9.8 μg of Der p	64.86% of the patients were clinically cured, 35.14% of them were effective Skin test index was significantly decreased in 78.4% of the patients after AIT
Zhao 2007 (15)	30 of asthma or/and AR patients were recruited Receive 1 years of SCIT PEF, the diameter of SPT	The mean age was 9.4 years (range, 5–17 years)	The PEF was significantly increased after AIT (P<0.01) The average wheal diameter of skin prick test was significantly decreased after AIT (P<0.01)
Xiang 2006 (16)	24 asthmatic subjects FEV_1, PEF were measured before and after 30 minutes of SCIT	The mean age was 8 years (range, 5–12 years). The maintenance dose was 9.8 μg of Der p	The FEV_1 and PEF were not significantly different between before and after 30 minutes of AIT
Wang 2005 (17)	30 AR subjects Receive 25 week of SCIT Symptom and sign scores were measured	Subjects between the ages of 6 and 60 years. The maintenance dose was 9.8 μg of Der p	A clinically significant reduction in symptom and sign score comparing with pre-treatment (P<0.01)

Table 1 (*continued*)

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Study	Study design	Characteristics of the participants and allergen for AIT	Main findings
Han 2007 (18)	55 AR subjects Receive 25 week of SCIT Symptom and sign scores were measured	The mean age was 35 years (range, 6–59 years). The maintenance dose was 9.8 μg of Der p	Symptom and sign score were significant reduced compared with pre-treatment (P<0.01)
Fan 2016 (19)	24 AR subjects Receive 1–3 years of SCIT Total 5 symptom score were measured	The mean age in SCIT group was 28 years	The mean total 5 symptom score of AIT group was significantly lower than that of untreated group (P<0.01)
Zhao 2016 (20)	69 AR and/or asthma subjects Receive 1 year of SCIT Symptom scores and medication scores were measured	The mean age was 7 years (range, 5–14 years). The maintenance dose was 9.8 μg of Der p	The AIT group showed a significant reduction in symptom scores after 4 and 12 months of AIT (P<0.0001 for both time points) compared to the control group
Lai 2013 (12)	335 AR and/or asthma subjects Receive 3 year of SCIT Symptom scores and medication scores, FEV_1 were measured	226 children (age ≤14 years) and 109 adults (age 15–64 years). The maintenance dose was 9.8 μg of Der p	Children are more responsive to AIT, demonstrating clinical (symptom and medication scores) and FEV_1 improvement during a shorter AIT period compared to adults

The visual analog scale: The visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. SPT, skin prick test; Der p, *Dermatophagoides pteronyssinus*; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; SMS, combined symptom medication scores; AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; PEF, peak expiratory flow; AR, allergic rhinitis; AHR, airway hyperresponsiveness.

differences between active SCIT and placebo patients. The improvement in non-specific airway hyperresponsiveness was also comparable between the two groups. These results may be related to the regular usage of ICS in most of the patients included in the study. However, after the patients were given 2–3 years of SCIT treatment, their non-specific airway hyperresponsiveness gradually decreased, even returning to normal in some patients. This result indicated that the amelioration of airway inflammation may take longer than symptom improvement, and it explained why SCIT must be taken for 3–5 years. One study by Wang *et al.* (13) showed that after 25 weeks treatment, pulmonary function indexes of pediatric patients with asthma were significantly improved.

Specific allergen sensitivity

Many studies have demonstrated reductions of skin responses to allergen prick test used to assess sIgE-mediated immediate allergic reactions. Wang *et al.* (13) showed skin indexes (SI) to HDM after 1 year were significantly reduced in patients treated with SCIT than those with placebos. After 2–3 years, in patients with SCIT, SI was further decreased and significantly smaller than that before treatment, but serum HDM sIgE and eosinophil cationic protein (ECP) did not decrease after 3 years of treatment. Lin *et al.* (14) reported that after the patients were treated for 3 years, their serum HDM sIgE showed a trend towards decreasing but without statistical significance, while ECP was significantly decreased. Zhao *et al.* (15) also demonstrated a significant decrease in the average wheal diameter of SPT against HDM after the patients were treated with SCIT for 1 year.

Safety evaluation

In Chinese Guideline on AIT for AR (8), Bao *et al.* compared the classifications of systemic reactions

between guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) (21) and World Allergy Organization (WAO) (22) for AIT and summarized them in five grades, of which Grade 0 with no symptoms or nonspecific symptoms, Grade I with mild systemic reactions, Grade II with moderate systemic reactions, Grade III with severe (non-life-threatening) systemic reactions, Grade IV with anaphylactic shock that symptoms/signs presenting in more than one organ or system, and Grade V with severe systemic reactions causing death. According to the results of studies performed in other countries, the prevalence of systemic adverse reactions ranges from 3.7% to 5.2% in all patients who had received SCIT, which is about 0.093% to 0.3% of the total number of injections (23), and the incidence of severe fatal systemic adverse reactions is one event per 1 to 2.5 million injections (24-26). In a study reported by Zeng *et al.* (27), among 15,645 injections, immediate local and systemic adverse reactions occurred in 8,523 (54.5%) and 397 (2.5%) injections respectively, this result is in accordance with the literatures. Most of the reactions occurred within 30 min of the injection. The symptoms were mild and the responses to treatment were good. No serious adverse reaction was noted. Since the incidence of systemic adverse reactions is higher during the up-dosing phase than the maintenance phase, Xiang *et al.* (16) studied the tolerances to the allergen vaccine of SCIT in 24 pediatric patients with mild to moderate allergic asthma during the up-dosing phase. They found that the incidence of systemic adverse reaction was 3.7%. Most of these were late reactions and all of which were Grade II reactions. The incidence of local adverse reactions was 14.9%, and most were mild. Local reactions showed no predictive values for systemic reactions. A study by Wang *et al.* (13) revealed an incidence of 0.7% for systemic adverse effect in pediatric patients, indicating the allergen vaccine is of low rate of reactions for the treatment of pediatric allergic asthma.

In the studies by Zeng *et al.* (27), Wang *et al.* (17), Han *et al.* (18), and Liu *et al.* (28), the incidence of systemic adverse reactions was 0.57–2.4% for a conventional injection schedule used to treat AR. Zhang *et al.* (10) administered a total of 3,464 injections to AR patients with the cluster injection schedule. The incidence of systemic adverse reactions was 5.9% and 0.75%, respectively, for the total number of patients and injections. This result is slightly higher than reported. Most of the systemic adverse reactions occurred during the up-dosing phase, which accounted for 3.9% and 0.71%, respectively, of the total number of patients and injections. The prevalence of Grade III reactions that required adrenaline treatment was around 0.12% of the total injections (17,18,27,28). In accordance to studies performed in other countries, no Grade IV reaction occurred. Most of the adverse reactions occurred in patients with asthma. Therefore, asthma is the main risk factor of systemic adverse reaction to SCIT. According to guidelines from China, EAACI and WAO, SCIT cannot be given in patients with unstable asthma or FEV_1 lower than 70% of the expected value. All patients reported with systemic adverse reactions achieved rapid remission when treated and no hospitalization was required, indicating that SCIT is safe both in conventional and cluster schedule (*Table 2*). Nevertheless, GINA guideline emphasizes that AIT must be weighed against the risk of side effects in patients with asthma (1). EAACI position paper (21) gives the instruction that the scheduled allergen dose should be reduced in case of a systemic reaction at the preceding visit. The magnitude of reduction depends on the severity of the reaction. In case of anaphylactic and other life-threatening reactions the continuation of SCIT should be carefully evaluated.

Mechanisms underlying SCIT

The mechanisms that are associated with AIT involve antibody responses and cellular reactions. Wang *et al.* (29) evaluated T helper cell-secreted cytokines and DNA methylation patterns in children treated with Der p AIT, they found decreased IL-2 production and increased IL-4 cytokine promoter methylation. Fan *et al.* (19) investigated the response of group 2 innate lymphoid cells (ILC2s) of peripheral blood in HDM-sensitized Chinese patients with AR who received SCIT with Der p extract, they found the levels of ILC2s in the peripheral blood of immunotherapy group were significantly reduced compared with that in untreated group, and suggested that the relatively high level of ILC2s in AR patients sensitized to HDM may be treated by Der p SCIT, and a reduction of ILC2 levels might contribute to symptom remission and immunologic tolerance in AR. Zhao *et al.* (20) found that IgG4 and IgE blocking factor correlated with symptoms at 12 months of SCIT, where the assay of IgE blocking factor measured the blocking activity of IgE and allergen binding. Feng *et al.* (11) found that Der p sIgG4 in SCIT patients significant increased from week 12 to 156, and serum obtained from SCIT patients significantly inhibited Der p sIgE binding to B cells after 16 weeks. Luo *et al.* (30) found microRNAs and Foxp3 mRNA was significantly increased after 3 months

Table 2 The recent study outcomes of AIT adverse reactions in China

Study	Study design	Characteristics of the participants and allergen for AIT	Adverse reactions
Wang 2006 (7)	A double-blind, placebo-controlled study involving 132 asthmatic subjects 52 weeks of SCIT	Subjects between the ages of 6 and 45 years. The maintenance dose was 9.8 μg of Der p	Seven (0.4% of all injections) grade 1, 71 (4.8%) grade 2 and 7 (0.5%) grade 3 reactions in the AIT group; 2 (0.1%) grade 1 and 25 (1.7%) grade 2 reactions in the placebo group (P<0.001)
Qi 2016 (9)	284 AR subjects Receive 3 year of SCIT	The mean age was 17.6 years (range, 5–65 years). The maintenance dose was 4.5 μg of Der p	Local adverse reaction in the AIT responder group (82.3%) higher than the non-responder group (47.4%) (P<0.0001) Systemic adverse reaction was no different between the AIT responder group (14.3%) and the AIT non-responder group (9.2%) (P=0.367)
Zhang 2008 (10)	154 patients with allergic rhinitis to Der p were allocated Receive 1 year of cluster AIT	The mean age was 24 years (range, 6–62 years). The maintenance dose was 9.8 μg of Der p	Systemic adverse reactions (0.75% of all injection, 5.9% of all patients)
Wang 2006 (13)	68 asthmatic subjects Receive 25 week of SCIT	The mean age was 8 years (range, 5–14 years)	Local adverse reactions (2.4%), systemic reactions (0.7%)
Lin 2007 (14)	37 patients of AR combining with mild-moderate asthma were recruited Receive 3 years of SCIT	The mean age was 20 years (range, 6–49 years). The maintenance dose was 9.8 μg of Der p	Local adverse reactions (14.9%), systemic adverse reactions (3.7%)
Xiang 2006 (16)	24 asthmatic subjects Observe up-dosing phase of SCIT	The mean age was 9.4 years (range, 5–17 years)	Immediate side-effects (7.3% of all injection, 58.33% of all patients), late side-effects (10.27% of all injection, 23.68% of all patients)
Wang 2005 (17)	30 AR subjects Receive 25 week of SCIT	Subjects between the ages of 6 and 60 years. The maintenance dose was 9.8 μg of Der p	Local adverse reactions (16.25%), systemic reactions (1.41%)
Han 2007 (18)	55 AR subjects Receive 25 week of SCIT	The mean age was 35 years (range, 6–59 years). The maintenance dose was 9.8 μg of Der p	Local adverse reactions 16.62%, systemic reactions (0.57%)
Liu 2017 (28)	429 asthma subjects Receive SCIT	Subjects between the ages of 5 and 17 years. The maintenance dose was 9.8 μg of Der p	2.59% systemic reactions in all injections, 15.62% systemic reactions in all patients
Zeng 2013 (27)	462 asthma and/or AR subjects Receive SCIT	The median age was 13 years. The maintenance dose was 9.8 μg of Der p	Local adverse reactions (54.5% of all injection, 58.33% of all patients), systemic adverse reactions (2.5% of all injection, 33.1% of all patients)

AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; AR, allergic rhinitis; Der p, *Dermatophagoides pteronyssinus*.

Table 3 The recent study outcomes of AIT mechanism in China

Study	Characteristics of the participants and allergen for AIT	Biomarkers	Main findings	Main mechanisms involved
Feng 2018 (11)	35 children (age ≤14 years) and 48 adults (age 15–57 years). The maintenance dose was 9.8 μg of Der p	Der p-sIgG4; Der p-sIgE facilitated allergen binding to B cells	Der p sIgG4 in SCIT patients significant increased; serum obtained from SCIT patients significantly inhibited Der p sIgE binding to B cells	Induced productions of blocking antibodies
Lin 2007 (14)	The mean age was 20 years (range, 6–49 years). The maintenance dose was 9.8 μg of Der p	tIgE, sIgE, IgG, ECP, eosinophil counts; IL-4, IL-5, IFN-γ	tIgE, ECP and eosinophil counts in peripheral blood of the patients were significantly reduced compared to before SIT (P<0.01) IL-4 and IL-5 were decreased to normal, IgG and IFN-γ were increased	Down regulated numbers of B cell, eosinophils and Th2 function. Up-regulated Th1 function. Induced blocking antibodies production
Zhao 2007 (15)	The mean age was 9.4 years (range, 5–17 years)	The wheal diameter of SPT	The diameter of SPT is significantly decreased after 1 year of SCIT (P<0.01)	Down-regulated skin sensitivity
Wang 2017 (29)	Subjects between the ages of 6 and 18 years. The maintenance dose was 300 AU of Der p	Cytokines and DNA methylation patterns	Der p-specific IL-2, IL-4 and IL-5 cytokine levels were significantly decreased by SCIT DNA methylation of cytokine genes, particularly IL-4, was increased after SCIT	Down-regulated Th2 function, and up-regulated Th1 function
Fan 2016 (19)	The mean age in SCIT group was 28 years	The response of ILC2s	SCIT group vs. untreated group (P<0.001), SCIT group vs. healthy controls (P=0.775)	Reduced ILC2s, down-regulated Th2 function
Zhao 2016 (20)	The mean age was 7 years (range, 5–14 years). The maintenance dose was 9.8 μg of Der p	IgG4 and IgE blocking factor	Der p IgG4 increased after 4 months of SCIT, and correlated to symptom scores at 12 months Der p IgE-blocking factor increased after 4 months of SCIT, and correlated with symptom scores at 4 months	Induced productions of blocking antibodies
Luo 2016 (30)	The mean age in SCIT group was 6.5 years	miR-146a and Foxp3 mRNA; TRAF6 protein; IL-5, IL-10	miR-146a and Foxp3 mRNA was significantly increased after SCIT (P<0.01) The TRAF6 protein level and serum IL-5 level were significantly decreased (P<0.01)	Regulated immune cell differentiation and TRAF6-mediated signalling in inflammatory settings
Zeng 2016 (31)	Subjects between the ages of 5 and 16 years. The maintenance dose was 9.8 μg of Der p	Der p-sIgE, Der p-sIgG4; Der p-sIgE/sIgG4 ratio	sIgG4 levels for Der p, Der p 1 and Der p 2 were increasing after SCIT The sIgE/sIgG4 ratios for Der p 1 and Der p 2 decreased from 6 months of SCIT	Induced productions of blocking antibodies
Lai 2013 (12)	226 children (age ≤14 years) and 109 adults (age 15–64 years). The maintenance dose was 9.8 μg of Der p	Der p-sIgG4	The increase ratio of Der p-sIgG4 was higher in children than adults at 52 weeks (P<0.001) and 104 weeks (P=0.0156) of SCIT	Induced productions of blocking antibodies

tIgE, total IgE; sIgE, specific IgE; sIgG, specific IgG; Der p, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; SPT, skin prick test; ILC2s, group 2 innate lymphoid cells; TNF, tumor necrosis factor; TRAF, TNF receptor associated factor; AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy.

of SCIT and SLIT in children with persistent AR. Zeng *et al.* (31) investigated the serum specifics IgE and sIgG4 to allergen component of Der p, they found the Der p 1 and Der p 2 sIgE levels were elevated at 6 months and progressively declined from 12 months, and the sIgG4 levels for Der p, Der p 1 and Der p 2 were increasing during the first year and reached a plateau thereafter. Lai *et al.* (12) found the levels of Der p-specific IgG4 significant increase after 10 weeks of subcutaneous AIT, and the increase ratio of Der p-specific IgG4 was higher in children than adults at 52 weeks and 104 weeks of AIT (*Table 3*).

Conclusions and practical considerations

A 1- to 3-year administration of the standardized subcutaneous injection of HDM vaccine as recommended by the GINA, EAACI, WAO and China guidelines, in patients with AR and mild to moderate allergic asthma can significantly improve rhinitis and asthma symptoms, reduce the need for medication, and decrease skin sensitivity to HDM. SCIT can also maintain stable pulmonary functions in all patients, improve pulmonary function in pediatric patients and reduce non-specific airway hyperresponsiveness. The safety of this allergen vaccine in Chinese patients is similar to that reported in foreign studies. Successful AIT may induce antibody responses and cellular reactions. The studies of AIT in China suggest AIT with standardized allergen vaccine can ensure the efficacy and safety in patients with allergic diseases when the guidelines are closely followed and the indications and contradictions of treatment are adhered carefully.

Among current AR and asthma therapies, AIT is the only therapy that can change the underlying natural history of the allergic conditions. However, before the physicians decide to apply AIT to patients, the following considerations must be taken into account (8,21,22):

- Clinical symptoms of the patients are induced predominantly by allergen exposure;
- Using standardized products with documented clinical efficacy and safety is strongly recommended;
- AIT should be prescribed only by an allergist-immunologist or other physician who is expertly trained in the therapy;
- AIT should be administered under the supervision of an allergist-immunologist or other physician specifically trained in immunotherapy, the early signs and symptoms of anaphylaxis, and appropriate emergency procedures and medications;
- SCIT should be given only in facilities equipped to treat anaphylaxis;
- The health status of the patient should be evaluated prior to every injection. Patients who are acutely ill, especially with asthma or respiratory difficulties, should not receive immunotherapy until their disease is stabilized;
- Patients should always be asked about current medications prior to immunotherapy, to avoid interactions with beta blockers and other conflicting medications;
- Patients must wait at the health care facility a minimum of 30 min after an allergen injection. The time period may be extended for high-risk patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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