A 2-year step-down withdrawal from inhaled corticosteroids in asthmatic children receiving immunotherapy

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Original article

Background: **Inhaled corticosteroids (ICSs) for treating asthma are controversial because of their negative effects on the growth of asthmatic children and without clearly defined withdrawal strategy. A 2-year ICS step-down and withdrawal strategy has been developed for asthmatic children receiving 3-year subcutaneous immunotherapy (SCIT).**

Methods: **Eleven children were included into the SCIT group and 13 children into the ICS group. ICSs were discontinued when children met the following criteria: requiring only 1 puff per day, with good control, for at least 6 months; having a forced expiratory volume in 1 second (FEV_1)/forced vital capacity ≥80%; and SCIT discontinued for ≥24 months. The main endpoints were the results of both the childhood asthma control test (C-CAT) and the methacholine bronchial provocation test.**

Results: **In the SCIT group, all the 11 children had ICS discontinued, with one child developed asthma attack after pneumonia and received ICS again after completion of SCIT. In the ICS group, five children discontinued ICS and developed asthma attacks later and received ICS again; the other eight children developed severe symptoms during ICS step-down. Thus, the discontinuation of ICS was only achieved in the SCIT group. The dose of methacholine that caused a decrease of 20% in FEV_1 continued to improve after discontinuation of ICS for the SCIT group and presented better results than the ICS group (P=0.050). After completion of SCIT, the C-CAT had improved significantly after 30 months of treatment compared with the ICS group (P<0.05).**

Conclusion: **In the present study, we developed a 2-year step-down and withdrawal strategy from ICSs strategy for allergic asthma children receiving SCIT; the strategy was efficacious and safe.**

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Key words: **allergy; asthma; immunotherapy; inhaled corticosteroid**

Introduction

Allergy immunotherapy in children with asthma is still under debate in terms of its efficacy and risks. The benefits of immunotherapy for lung function have not been confirmed; in fact, symptoms deteriorate in a certain portion of patients.[1] More specifically, the efficacy of house dust mite (HDM) immunotherapy is promising in the field of asthma control.[2,3] To optimize on the benefits of this therapy in children, it will be necessary to improve the management of those patients who benefit from it. One critical issue in this debate is the timing of withdrawal from inhaled corticosteroids (ICSs).

Withdrawal of ICSs is a controversial topic in asthma treatment, especially when it concerns children; after all, ICSs can endanger the growth of children in height.[4] However, complete cessation of ICSs is necessarily followed by an increased risk of exacerbations. One study[5] involving adult patients showed that bronchial hyperresponsiveness and sputum eosinophils may be useful in guiding the reduction of ICS doses. Of course, these results cannot necessarily be applied directly to children with allergic asthma who are receiving immunotherapy.

Previous studies on HDM allergy immunotherapy have mainly been focused on the efficacy rather than

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the timing of ICS discontinuation. We developed a 2-year strategy of step-down and withdrawal from ICSs after initialization of the 3-year HDM immunotherapy program. In the present study, we compared the efficacy and safety of this ICS withdrawal strategy among children with or without HDM allergy immunotherapy.

Methods

Patients

In the period between June and December 2011, 28 consecutive children with HDM-related allergic asthma were enrolled into the present study. Their persistent asthma was diagnosed on the basis of the Global Initiative for Asthma (GINA) guidelines. Sensitivity to HDM was confirmed when the skin-prick test (SPT) elicited a positive response (≥2+) to HDM extract, or when serum was positive for immunoglobulin E (IgE) specific to either *Dermatophagoides pteronyssinus* (Der p) or *D. farinea* (Der f; ≥4). Before the initiation of HDM subcutaneous immunotherapy (SCIT), the children's symptoms were well controlled; specifically, the children scored ≥19 on the childhood asthma control test (C-CAT), and their resting forced expiratory volume in 1 second (FEV_1) was at least 80% of their forced vital capacity (FVC; FEV_1/FVC ≥80%). None had any contraindications for SCIT and none required medication for allergic rhinitis (AR). We did not exclude patients with concomitant sub-cardinal perennial allergens, such as cat, dog dander, *Alternaria* spp. and cockroach, because most had many such hypersensitivities. Two children were excluded because of rejection of lung function tests after 1 year of treatment. The study was approved by the Ethical Committee of the Guangzhou Medical University, as well as the Guangzhou Women and Children's Medical Center Hospital; written informed consent was obtained from the patients' parents.

The skin-prick test

The SPT was performed using a standard aeroallergen panel of Der p and Der f (ALK-Abello AS, Denmark). A drop of each allergen extract was introduced, via lancets, into the skin on the volar side of the forearm. Histamine (10 mg/mL) and glycerinated saline were used as positive and negative controls, respectively. Fifteen minutes later, the mean largest wheal diameter, as well as the mean diameter perpendicular to the largest, was recorded as the response. A response of ≥3 mm greater than the saline control was deemed positive. Before the test, we excluded the influential factors and took an accurate record of each allergen and its wheal diameter in each child. We calculated the skin index as the ratio of allergen wheal diameter to the histamine wheal diameter, such that the SPT result from each allergen was also defined in terms of the skin index: ≤0.5 (+), >0.5 and ≤1.0 (2+), >1.0 and ≤2.0 (3+) and >2.0 (4+).

Pulmonary function measurements

Pulmonary function was measured using plethysmography and computerized spirometry (Masterlab Yaeger, Wurtzburg, Germany). Also measured were FVC, FEV_1, peak expiratory flow (PEF), maximal expiratory flow (MEF), and MEF at 25%, 50% and 75% of FVC (MEF25, MEF50 and MEF75, respectively) for small airways. In addition, FEV_1/FVC was calculated. The results of the methacholine bronchial provocation test (MBPT) were the main endpoint of this study; the test was carried out each year. A dosimeter (Yaeger) activated by inhalatory effort was used to administer increasing doses of methacholine (0-2.5 mg). The dose of methacholine that caused a decrease of 20% in FEV_1 was defined as the PD20. The MBPT was considered negative when the PD20 was greater than 2.5 mg.

Immunotherapy

Specific SCIT was performed using Alutard R SQ Der p (ALK-Abello AS, HΦsholm, Denmark), a standardized aluminum hydroxide-absorbed Der p. Thirteen patients were enrolled into the SCIT group, and the other 15 recieved conventional ICS. The 3-year SCIT treatment consisted of a 15-week up-dosing, followed by a maintenance stage that lasted for the rest of the 3 years. SCIT was initiated at a dose of 20 SQ units, which was increased weekly until a target maintenance dose of 100 000 SQ units was reached. Once this dose was reached, injection intervals were 4 weeks for the first year, 5 to 6 weeks for the second year, and 7 weeks for the last year. The researchers could adjust the injection dosage in response to the child's local and systematic reactions without alternation of the cumulative allergen dosage.

ICS step-down and withdrawal strategy

All children were given ICSs (fluticasone propionate or budesonide) combined with an inhaled, long-acting β_2-agonist (LABA) and leukotriene receptor antagonists. One child was given fluticasone propionate without LABA, and another had leukotriene receptor antagonist (LRA) discontinued due to side effects. Their ICS dosages were all low according to the GINA guidelines. To compare the dosages of the two ICS types, we calculated the daily low dose (DLD) using the following formulas: DLD of fluticasone propionate=dosage of fluticasone propionate/100 μg and DLD of budesonide=dosage of budesonide/200 μg.

The stepping-down strategy involved discontinuing LRA when good control had been maintained for more than 3 months and the patient had undergone SCIT for at least 6 months; ICS and inhaled LABA were stepped down when good control had been maintained for more than 3 months, and when LRA had not been given for at least 3 months; ICS and inhaled LABA

were discontinued when the children met the following criteria: 1) requiring only 1 puff per day, with good control, for at least 6 months; 2) having an FEV_1/FVC ≥80%, and 3) having been undergoing SCIT for about 24 months. If symptoms deteriorated, the researchers adjusted the drugs based on individual symptoms and asthma control levels.

Data collection and follow-up

Before treatment, blood samples were taken to assess serum Der p specific IgE (sIgE), Der f sIgE, and total IgE (tIgE) antibody levels using a fluoroimmunoassay (UniCAP®, Pharmacia Diagnostics, Uppsala, Sweden). The absolute blood eosinophil counts were determined using an automatic cytoanalyzer (Mindray®, Shenzhen, China) with the normal value set at $\leq 0.52\times10^9$/L. Fractional exhaled nitric oxide (FeNO) was measured using the NObreath® (Bedfont Scientific, Maidstone, Kent, UK) and following the American Thoracic Society/European Respiration Society recommendations.[6] Serum eosinophil cationic protein (ECP) was measured using a commercial fluoroimmunoassay kit (Pharmacia ECP UniCAP System FEIA®, Pharmacia Diagnostics, Uppsala, Sweden), wherein a concentration of ≥0.35 IU/mL was considered abnormal.[7] C-CAT was conducted before the initiation of SCIT, as well as every 3 months subsequently, to evaluate asthma control. Pulmonary function measurements and MBPT were conducted before SCIT initiation, as well as every year subsequently, to evaluate the safety of the step-down from medication.

We conducted a routine follow-up before each allergen injection and recorded the following in detail: nycterohemeral symptoms (both rhinitis and pulmonary symptoms), concomitant medications [e.g., oral second-generation antihistamine, ICS, LRA, and inhaled short-acting β_2-agonists (SABA)], and adverse reactions (immediate/late and local/systemic). All children were followed up regularly, either at the clinic or by telephone, for at least one year after completing the treatment.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. Data were reported as median and range when distribution was not normal. Statistical differences in clinical characteristics between the two groups were compared using the Student's *t* test, the Mann-Whitney *U* test, and Fisher's exact test. Group comparison tests were performed using the Wilcoxon rank-sum test. For all tests, a *P* value <0.05 was considered statistically significant, and all *P* values quoted are 2-sided. Statistical analyses were performed using SPSS v. 20.0 (SPSS Inc., Chicago, IL, USA).

Table. Baseline demographic and clinical characteristics of asthmatic children receiving HDM SCIT and ICS

Characteristics	ICS (*n*=13)	SCIT (*n*=11)	*P*
Gender, *n* (%)			
Male	9 (69.2)	6 (54.5)	0.675
Female	4 (30.8)	5 (45.5)	
Age (y), median (range)	8 (5-14)	8 (5-12)	-
Family history, *n* (%)	13 (100)	10 (90.9)	0.458
History of breast-feeding, *n* (%)	9 (69.2)	8 (72.7)	0.999
ICS before SCIT (mon), median (range)	NA	10 (1-24)	NA
Start mon of SCIT, median (range)	NA	8 (6-12)	NA
Der p SPT, *n* (%)			
0	1 (7.7)	1 (9.1)	0.498
1+	2 (15.4)	0 (0.0)	
2+	0 (0.0)	1 (9.1)	
3+	4 (30.8)	5 (45.5)	
4+	6 (46.2)	4 (36.4)	
Der f SPT, *n* (%)			
1+	1 (7.7)	1 (9.1)	0.836
2+	2 (15.4)	3 (27.3)	
3+	7 (53.8)	4 (36.4)	
4+	3 (23.1)	3 (27.3)	
tIgE (IU/mL), median (range)	549 (66-3390)	469 (174-3830)	0.839
Der p-sIgE (IU/mL), median (range)	56.3 (0-100)	88.4 (18-100)	0.207
Der f-sIgE (IU/mL), median (range)	73.1 (2-100)	100.0 (41-100)	0.033
ECP (IU/mL), median (range)	53.6 (16-100)	33.7 (8-78)	0.132
Blood eosinophil count ($\times10^9$/L), median (range)	0.37 (0.10-0.70)	0.29 (0.01-0.65)	0.212
Pulmonary function measurements, median (range)			
FVC, % of predicted	106 (90-133)	100 (75-119)	0.338
FEV_1, % of predicted	90 (74-130)	91 (85-111)	0.816
FEV_1/FVC, %	82 (67-86)	83 (74-87)	0.308
PEF, % of predicted	106 (59-138)	89 (63-107)	0.223
MEF, % of predicted	80 (49-140)	94 (64-110)	0.885
MEF25, % of predicted	60 (36-117)	64 (33-106)	0.562
MEF50, % of predicted	66 (44-124)	78 (61-107)	0.164
MEF75, % of predicted	79 (49-134)	88 (63-102)	0.954
PD20 (mg), median (range)	0.395 (0.038-2.010)	0.213 (0.023-1.840)	0.156
FeNO (ppb), median (range)	32 (12-147)	46 (17-84)	0.384
ICS duration (mon), median (range)	36 (26-36)	24 (23-30)	<0.001
Accumulative ICS (DLD), median (range)	610 (450-1481)	730 (328-1138)	0.749
Accumulative SABA (mg), median (range)	500 (0-3000)	600 (0-2500)	0.536
Discontinuation of ICS, *n* (%)	0 (0.0)	10 (90.9)	<0.001

HDM: house dust mite; SCIT: subcutaneous immunotherapy; ICS: inhaled corticosteroid; Der p: *Dermatophagoides pteronyssinus*; Der f: *Dermatophagoides farinea*; SPT: skin-prick test; tIgE: total immunoglobulin E; sIgE: specific immunoglobulin E; ECP: eosinophil cationic protein; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; PEF: peak expiratory flow; MEF: maximal expiratory flow; MEF25, 50, 75: MEF at 25%, 50% and 75% of FVC, respectively; PD20: the dose of methacholine that caused a decrease of 20% in FEV_1; FeNO: fractional exhaled nitric oxide; DLD: daily low dose; SABA: short-acting β_2-agonists; NA: not available.

Results

Patient characteristics

Thirteen children (6 boys and 5 girls) were included into the SCIT group and received SCIT and ICS step-down and withdrawal procedure, and two were lost to follow-up. Fifteen children (9 boys and 4 girls) were enrolled into

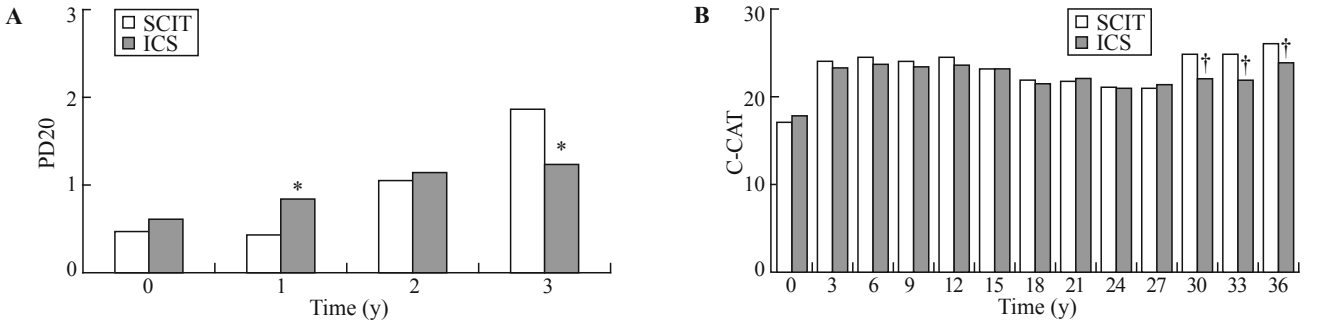

Fig. 1. Change in PD20 (**A**) and C-CAT (**B**) during house dust mite subcutaneous immunotherapy. *: $P<0.1$; †: $P<0.05$. SCIT: subcutaneous immunotherapy; ICS: inhaled corticosteroid; PD20: the dose of methacholine that caused a decrease of 20% in FEV_1; C-CAT: childhood asthma control test score.

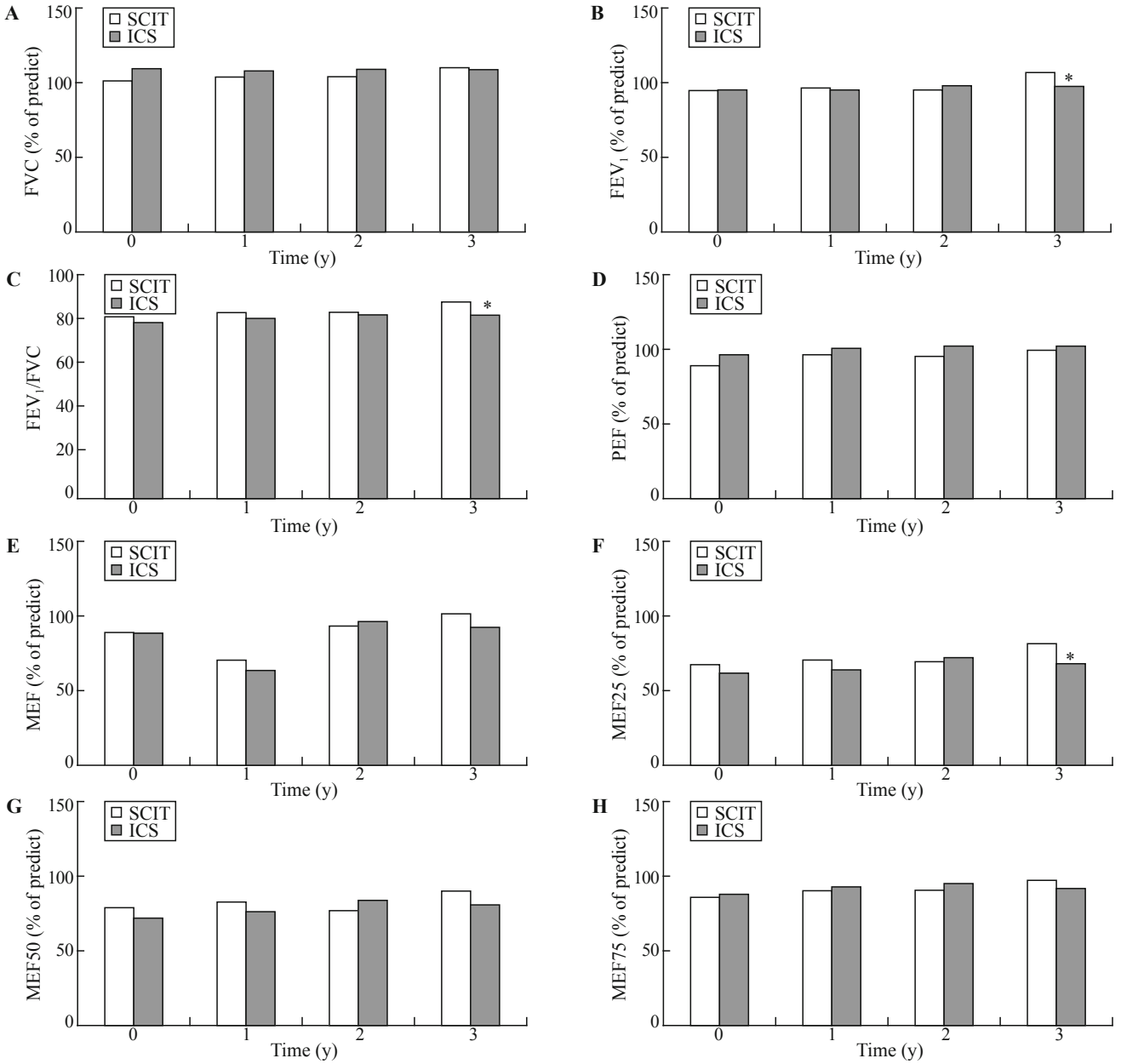

Fig. 2. Change in pulmonary function measurements during house dust mite subcutaneous immunotherapy. *: $P<0.1$. **A**: Forced vital capacity (FVC), % of predicted; **B**: Forced expiratory volume of 1 second (FEV_1), % of predicted; **C**: FEV_1/FVC; **D**: Peak expiratory flow (PEF), % of predicted; **E**: Maximal expiratory flow (MEF), % of predicted; **F**: MEF at 25% of FVC, % of predicted; **G**: MEF at 50% of FVC, % of predicted; **H**: MEF at 75% of FVC, % of predicted. SCIT: subcutaneous immunotherapy; ICS: inhaled corticosteroids.

the ICS group and received ICS step-down and withdrawal procedure; two patients were lost to follow up. Ten (90.9%) patients in the SCIT group and 13 (100.0%) in the ICS group had a family history of allergic diseases such as AR, asthma and dermatitis. The levels of clinical parameters, including age, breast feeding, Der p sIgE, Der f sIgE, tIgE, SPT, blood eosinophil count, ECP, FeNO, PD20 and all the parameters in lung function tests were similar between the two groups. In the SCIT group, before SCIT children were given asthma control medication for a median of 10 months (range: 1-24 months) (Table).

Discontinuation of ICS in the SCIT and ICS groups

In the SCIT group, all the 11 children had ICS discontinued; and one developed asthma attack after pneumonia and received ICS again after completion of SCIT. In the ICS group, five children discontinued ICS and developed asthma attacks later and received ICS again, with the other 8 children developed severe symptoms during ICS step-down. Thus, the discontinuation of ICS was only achieved in the SCIT group (Table).

The median ICS duration was 24 months (range: 23-24.5 months) before discontinuation of SCIT, with a cumulative DLD of 730 (range: 328-1137.5) for the SCIT group. For the ICS group, they were 36 months (range: 26-36 months) and 610 (range: 450-1481). The dosage of ICS and SABA was similar between the two groups (Table).

PD20 improvement between the SCIT and ICS groups

After one-year treatment, the SCIT group presented worse PD20 results compared with the ICS group (P=0.052). However, they displayed similar MBPT results with the ICS group after treatment for two years. Notably, the PD20 continued to improve after discontinuation of ICS for the SCIT group and presented better results than the ICS group (P=0.050) (Fig. 1A).

C-CAT improvement between the SCIT and ICS groups

C-CAT results were similar between the two groups after 27 months of treatment. C-CAT score deteriorated after 2 years of SCIT because of mild cough and rhinitis during discontinuation of ICS. In the SCIT group, decrease of C-CAT was not followed by exacerbation of asthma; this did not influence the step-down medication. After completion of SCIT, C-CAT improved significantly after 30 months of treatment compared with the ICS group (P<0.05) (Fig. 1B).

Pulmonary function measurements improvement between the SCIT and ICS groups

The results of pulmonary function measurements were similar during medication between the two groups. Furthermore, the FEV_1 of predictive value, FEV_1/FVC and MEF25 seemed to be improved after completion of SCIT in the SCIT group compared with the ICS group (P=0.092, 0.059 and 0.056, respectively) (Fig. 2).

Predictors of negative MBPT results

In the SCIT group, MBPT results were negative in nearly half of the children. Thus, it was necessary to identify the predictors of such results. We compared the characteristics of children who had shown a positive MBPT with those who had shown a negative MBPT and did not identify any significant prognostic factors. In addition, the cumulative dosages of ICSs were similar between groups. However, pulmonary function parameters, such as FVC, FEV_1, and PEF, at the cessation of ICS treatment displayed marginal significant predictive value (P=0.052 in each case; Supplementary Table).

Discussion

Withdrawal from ICSs that are used to treat asthma is a sensitive issue. Allergic asthma is caused by over-activation of the Th2 response to certain allergens.[8,9] However, ICSs is not a specific tretment that clearly targets the mechanism of asthma. Targeted therapies have been developed in recent years; namely, IgE inhibitors, antibody therapeutics that target interleukin-5 and interleukin-13 pathway, and allergic immunotherapy;[8] these treatments may lead to a cure for asthma in certain patient groups and make withdrawal from ICSs more feasible.[10,11] Withdrawal from ICSs is especially critical in children, because the drugs can endanger children's growth in height.[4] Step-down medication strategies for children receiving HDM immunotherapy have varied without consensus.[1-3,12,13] Moreover, withdrawal of ICSs has not been clearly mentioned in most studies. Therefore, we developed a 2-year medication step-down and withdrawal strategy for children receiving HDM SCIT, which was effective and safe for children receiving HDM SCIT.

Withdrawal of ICS was achieved only in the SCIT group, with none of the ICS group achieved persistent withdrawal of ICS. The results indicated that SCIT made allergic asthma a potentially curable disease and withdrawal of ICS could be reached in patients receiving SCIT. Besides, for HDM related allergic asthma, SCIT was an imperative remedy and ICS shall not be discontinued until SCIT was initiated for 2 years. In the present study, a critical period for children receiving HDM SCIT occurred 2 years after initiation of the treatment with decreased

C-CAT. However, these symptoms did not delay the step-down from medication or endanger the outcome.

In this study, we did not include patients who had received AR medication before SCIT. Clinically diagnosed AR is associated with significantly worse asthma control; specifically, children with physician-diagnosed AR are twice more likely to be hospitalized for asthma than those without.[14,15] Thus, children with asthma combined with severe rhinitis are more likely to experience exacerbation after withdrawal from ICSs. Moreover, medication for AR is complicated[14,16,17] and may therefore affect the efficacy of SCIT. For this reason, children who had received AR medication before SCIT were not included, and the sample size was not large as a result. Nonetheless, in the present study, children developed rhinitis around 2 years after SCIT, which decreased their C-CAT score. This phenomenon indicated the co-existence of mild rhinitis with asthma in these children. Significantly, short-term rhinitis was treated using oral H1-blockers and intranasal saline, and did not affect step-down medication or outcome. Importantly, the withdrawal strategy in the present study cannot be applied in children undergoing SCIT treatment for AR.

In conclusion, this report presents a 2-year step-down and withdrawal medication strategy for children with allergic asthma who are receiving HDM SCIT. The efficacy and safety of the withdrawal from ICSs was confirmed using pulmonary function tests and MBPT. However, this strategy needs to be validated in further studies with larger sample sizes.

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Ethical approval: The study was approved by the Ethical Committee of The Guangzhou Medical University, as well as The Guangzhou Women and Children's Medical center Hospital; written informed consent was obtained from the patients' parents.

Competing interest: No conflicts needed to be declared.

Contributors: He CH and Li X conceived and designed the project, analyzed the data, and drafted the initial manuscript. They contributed equally to this work. Lin JH, Xiao Q, Yu JL, Liu YF, Jiang WH and Chen C collected the data and participated in patient managment. Li X, Deng L and Zhou J interpreted the data and funded the project. All authors approved the final manuscript as submitted.

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