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ORIGINAL ARTICLE

Effects of subcutaneous and sublingual allergen immunotherapy on immune responses in children with bronchial asthma

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Abstract

Background: Allergic asthma in children significantly impacts quality of life, and immunotherapy, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), has emerged as an effective treatment. However, their comparative immunological mechanisms remain unclear.

Objective: This study aimed to compare the effects of SCIT and SLIT on immune response in children with allergic asthma and to explore their underlying immunological mechanisms.

Methods: A total of 86 children aged 5–12 years with allergic asthma who visited Hangzhou Children's Hospital were prospectively enrolled and randomly assigned to three groups: inhaled corticosteroids (ICS) group (n = 30), SCIT group (n = 30), and SLIT group (n = 26). Clinical and immunological parameters—including Childhood Asthma Control Test (C-ACT) scores, forced expiratory volume in the first second percentage (FEV1%), Th17, Treg cells, and serum levels of IL-17, IL-9, IL-10—were assessed before treatment and after one year.

Results: After treatment, all three groups showed significant improvements in C-ACT scores and FEV1% compared to baseline (all $p < 0.05$). The SCIT and SLIT groups demonstrated greater improvements than the ICS group (all $p < 0.05$), with no significant differences between the SCIT and SLIT groups ($p > 0.05$). In terms of immune markers, significant differences were observed in all parameters before and after treatment in the SCIT and SLIT groups (all $p < 0.05$), while Treg levels in the ICS group remained unchanged ($p > 0.05$). No statistically significant differences in immune markers were found among the three groups post-treatment (all $p > 0.05$).

Conclusion: Both SCIT and SLIT, when combined with ICS, offer superior efficacy compared to ICS monotherapy. The comparable immunological changes observed in SCIT and SLIT suggest a shared mechanism of immune tolerance, potentially mediated through Treg cell induction.

Key words: Subcutaneous immunotherapy, sublingual immunotherapy, inhaled corticosteroids, children, asthma

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Introduction

Bronchial asthma is one of the most common chronic inflammatory airway diseases in children, with a steadily increasing incidence worldwide. Allergic asthma represents the predominant phenotype, accounting for over 90% of pediatric asthma cases.[1] The current standard treatments include inhaled corticosteroids (ICS) and specific immunotherapy (SIT). While ICS is effective in controlling symptoms, it does not alter the natural course of the disease, and relapse often occurs after discontinuation.[2] SIT aims to induce immune tolerance by administering gradually increasing doses of allergen extracts to individuals with confirmed allergen sensitization, thereby reducing allergic symptoms and modifying disease progression.[3,4] SIT is typically used in conjunction with pharmacotherapy for managing allergic asthma and allergic rhinitis.[3,4]

Specific immunotherapy (SIT), which includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is recommended by both the National Asthma Education and Prevention Program Coordinating Committee (NAEPCC) and Global Initiative for Asthma (GINA) guidelines as an adjunct to standard treatment in children with allergic asthma.[5,6] Both modalities can effectively induce immune tolerance to allergens. However, the immunological mechanisms underlying these therapies are not yet fully elucidated. This study aims to compare the clinical outcomes and immunological profiles—specifically changes in Th17, Regulatory T (Treg) cells, and related cytokines—among children with asthma undergoing ICS, SCIT, or SLIT, to better understand the immune mechanisms of SIT and inform therapeutic strategies.

Materials and Methods

Study Participants

From January 2021 to December 2023, pediatric patients diagnosed with asthma and treated at Hangzhou Children's Hospital were recruited. After full disclosure of study details, the patients' guardians voluntarily selected SCIT, SLIT, or only ICS group participation based on family preference, the child's compliance, and economic considerations, and provided written informed consent. During the study period, all groups received standardized asthma management and regular follow-up following the GINA guideline recommendations. This study was reviewed and approved by the Medical Ethics Committee of Hangzhou Children's Hospital ([2020] Clinical Research Review No. 18) and registered in the National Medical Research Registration Information System of the People's Republic of China (MR-33-25-035115). It was conducted according to the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of all participating children.

Inclusion criteria were as follows: (1) Diagnosis of asthma according to the GINA guidelines, with no prior standardized antiasthmatic treatment; (2) Age between 5 and 12 years; (3) The sole or primary allergen was house dust mite, with a serum specific IgE (sIgE) level > 3.5 IU/mL (measured using an analyzer from Zheda Dixun Biological Gene Engineering Co., Ltd. Hangzhou, model DX-Blot 45 II), and a skin prick test (SPT) result of 3+ to 4+. The SPT result was determined according to the skin index (SI), calculated as: SI = allergen diameter/histamine diameter.[7] A 3+ reaction (strong positive) was defined as $1.0 \leq SI < 2.0$, and a 4+ reaction (very strong positive) as $SI \geq 2.0$[7] (4) Stable asthma with baseline forced expiratory volume in the first second percentage (FEV1) ≥ 80%; (5) Informed consent obtained from legal guardians.

Exclusion criteria included: (1) Previous treatment with house dust mite allergen extracts; (2) History of severe allergic reactions; (3) Current use of corticosteroids (Oral or intravenous administration of systemic glucocorticoids), immunosuppressants, or beta-blockers; (4) Comorbidities such as severe malnutrition, cardiovascular or cerebrovascular disease, autoimmune disorders, or psychiatric conditions; (5) Poor treatment compliance or inability to understand the risks and limitations of therapy.

Treatment Protocols

ICS group: Inhaled budesonide /formoterol powder inhaler (AstraZeneca AB, UK) was selected. The dosage was determined by specialists based on the individual condition of each patient. Patients received step-up or step-down ICS therapy according to GINA guidelines.

SCIT group: In addition to ICS patients received SCIT using standardized house dust mite extracts (Alutard-SQ®, ALK-Abelló, Denmark), administered alternately in both upper arms. The treatment consisted of an initiation phase and a maintenance phase. During the initiation phase, injections were given once weekly with gradually increasing doses: vials 1 to 3 were administered at 0.2, 0.4, and 0.8 mL, followed by vial 4 at 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 mL. During the maintenance phase, 1.0 mL of vial 4 was administered every 4–6 weeks. Patients were observed for 30 minutes after each injection.

SLIT group: Patients received SLIT in addition to ICS using standardized dust mite drops (Changdi®, WOLWOPHARMA Co., Ltd., China). Treatment included an initiation phase and a maintenance phase. During the first 3 weeks, patients received vials 1 (1 μg/mL), 2 (10 μg/mL), and 3 (100 μg/mL), respectively, with daily doses increasing from 1 to 10 drops. From week 4 onwards, vial 4 (333 μg/mL) was administered as three drops per day, held sublingually for 1–3 minutes before swallowing. Treatment duration was 12 months.

Outcome Measures

Childhood Asthma Control Test (C-ACT)

Children were followed up regularly, and C-ACT scores were completed by both the child and the guardian. The maximum score is 27; a score < 19 indicates uncontrolled asthma, 20–22 indicates partial control, and 23–27 indicates well-controlled asthma.

Lung Function

FEV1% was measured using a pediatric pulmonary function analyzer (MasterScreen, Jaeger, Germany).

Cytokine and Cell Profile Analysis

Peripheral venous blood samples (4 mL) were collected from all enrolled children before and after treatment to assess the expression levels of Th17, Treg, IL-17, IL-9, and IL-10.

Th17 and Treg Cell Analysis: 1 mL of anticoagulated venous blood was used for flow cytometric detection of Th17 and Treg cells (Th17 kits from MultiScience, catalog number A117H41042 and Treg kits from Beckman Coulter, catalog number 200511. Instrument: Navios, Beckman Coulter, USA), following the manufacturer's protocols.

Cytokine Levels (IL-17, IL-9, IL-10): 3 mL of non-anticoagulated venous blood was centrifuged at 3500 rpm for 5 min to collect serum. Cytokine levels were measured using ELISA (sandwich method) with kits from MultiScience (IL-17: A117H41042; IL-9: A109H41042;

IL-10: A110H41042). Absorbance was read using a Thermo Multiskan MK3 microplate reader (Thermo Fisher Scientific, USA).

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and compared using one-way ANOVA (inter-group) and paired *t*-tests (intra-group). Non-normally distributed data were expressed as median (P25, P75) and analyzed using Kruskal-Wallis H tests and Wilcoxon signed-rank tests. Pairwise comparisons were performed with Bonferroni post-hoc multiple comparisons. Categorical variables were expressed as percentages (%) and compared using the chi-square test. A $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 86 children with allergic asthma were enrolled in this study. After 1 year, three patients were lost to follow-up in the ICS group (final n = 30), 1 in the SLIT group (final n = 26), and none in the SCIT group (n = 30). The ICS group included 22 males and eight females with a mean age of 8.17 ± 1.57 years. The SLIT group comprised 19 males and seven females with a mean age of 8.22 ± 1.77 years. The SCIT group consisted of 21 males and nine females with a mean age of 8.16 ± 2.18 years. All three groups of pediatric patients received inhaled budesonide/formoterol via a dry powder inhaler (AstraZeneca AB, UK) at a dose of 80 μg per inhalation, twice daily. All patients achieved a well-controlled asthma status.

There were no significant differences in baseline characteristics among the three groups, including age, sex, disease duration, comorbidities, or asthma severity (all $p > 0.05$), as shown in **Table 1**.

Comparison of C-ACT Scores and FEV1% Before and After Treatment

Since the data were not normally distributed, the Kruskal–Wallis H test was used for intergroup comparisons. No significant differences among the groups in C-ACT scores ($H = 0.396$, $p = 0.820$) or FEV1% ($H = 0.821$, $p = 0.663$) before treatment. However, significant differences emerged after treatment in both C-ACT scores ($H = 9.638$, $P = 0.008$) and FEV1% ($H = 9.208$, $P = 0.010$). Bonferroni post-hoc multiple analysis indicated that both C-ACT and FEV1% improvements were significantly greater in the SLIT and SCIT groups compared to the ICS group (all $p < 0.05$), while no significant difference was observed between the SLIT and SCIT groups ($P = 0.497$ and $P = 0.825$, respectively), as shown in **Table 2**. Within-group comparisons showed significant improvements in C-ACT and FEV1% across all three groups after treatment (all $p < 0.05$).

Table 1. Baseline characteristics of the ICS, SLIT, and SCIT groups.

Characteristics	ICS (n = 30)	SLIT (n = 26)	SCIT (n = 30)	F or χ^2	*p*
Age (years)	8.17 ± 1.57	8.22 ± 1.77	8.16 ± 2.18	0.007	0.993
Gender (M/F)	22/8	19/7	21/9	0.101	0.951
Disease duration (years)	3.28 ± 1.05	3.33 ± 1.11	3.36 ± 1.17	0.039	0.961
Asthma severity (mild/moderate)	12/18	10/16	10/20	0.31	0.856
Allergic rhinitis (n)	20	18	21	0.084	0.959
Sensitization status (mono-sensitization / poly-sensitization)	16/14	15/11	17/13	0.121	0.941

Note: Asthma severity:
Mild asthma: defined as well-controlled asthma achieved with Step 1 or Step 2 treatment regimens.
Moderate asthma: defined as well-controlled asthma achieved with Step 3 or Step 4 treatment regimens.

Table 2. Comparison of C-ACT scores and FEV1% before and after treatment among the three groups.

Clinical parameters		ICS (n = 30)	SLIT (n = 26)	SCIT (n = 30)	H	*p*
C-ACT	Pre-treatment	15.00 (14.00, 16.00)	15.00 (14.00, 16.00)	15.00 (14.00, 16.00)	0.396	0.820
	Post-treatment	24.00 (22.00, 25.00) [a,▲]	25.00 (23.75, 26.25) [b,▲]	25.00 (24.00, 27.00) [b,▲]	9.638	0.008
FEV1%	Pre-treatment	90.70 (80.55, 101.93)	96.15 (84.53, 105.58)	92.20 (84.45, 101.40)	0.821	0.663
	Post-treatment	94.45 (90.15, 100.35) [a,▲]	102.60 (94.90, 108.40) [b,▲]	104.05 (95.63, 110.85) [b,▲]	9.208	0.010

Note: For the same parameter, groups sharing the same superscript letter are not significantly different. ▲indicates a significant within-group difference before and after treatment ($p < 0.05$).

Table 3. Comparison of Treg cells, Th17 cells, and cytokine levels before and after treatment in the three groups.

Clinical parameters		ICS (n = 30)	SLIT (n = 26)	SCIT (n = 30)	H	*p*
Treg (%)	Pre-treatment	6.82 (5.77, 8.01)	5.45 (4.46, 8.01)	6.21 (5.19, 7.02)	4.757	0.093
	Post-treatment	7.06 (5.60, 7.60)	6.72 (5.56, 8.80) ▲	7.82 (6.47, 8.48) ▲	3.012	0.222
Th17 (%)	Pre-treatment	0.77 (0.58, 1.53)	0.90 (0.73, 1.38)	0.97 (0.77, 1.64)	3.586	0.166
	Post-treatment	0.52 (0.38, 0.98) ▲	0.54 (0.34, 0.98) ▲	0.66 (0.42, 0.98) ▲	0.159	0.924
IL-17 (pg/ml)	Pre-treatment	20.29 (10.08, 4.89)	18.87 (11.39, 34.14)	18.52 (16.23, 23.08)	0.120	0.942
	Post-treatment	9.57 (6.18, 45.02) ▲	16.59 (8.46, 23.82) ▲	14.39 (11.82, 17.58) ▲	1.708	0.426
IL-10 (pg/ml)	Pre-treatment	5.80 (3.81, 8.77)	4.58 (2.57, 6.24)	4.16 (2.47, 7.22)	3.718	0.156
	Post-treatment	8.21 (5.36, 12.30) ▲	7.52 (3.95, 12.34) ▲	5.27 (3.81, 10.18) ▲	2.938	0.23
IL-9 (pg/ml)	Pre-treatment	0.59 (0.44, 0.62)	0.50 (0.42, 0.64)	0.58 (0.47, 0.63)	0.856	0.652
	Post-treatment	0.40 (0.30, 0.46) ▲	0.38 (0.33, 0.46) ▲	0.37 (0.30, 0.44) ▲	0.536	0.765

Note: ▲indicates a significant within-group difference before and after treatment ($p < 0.05$)

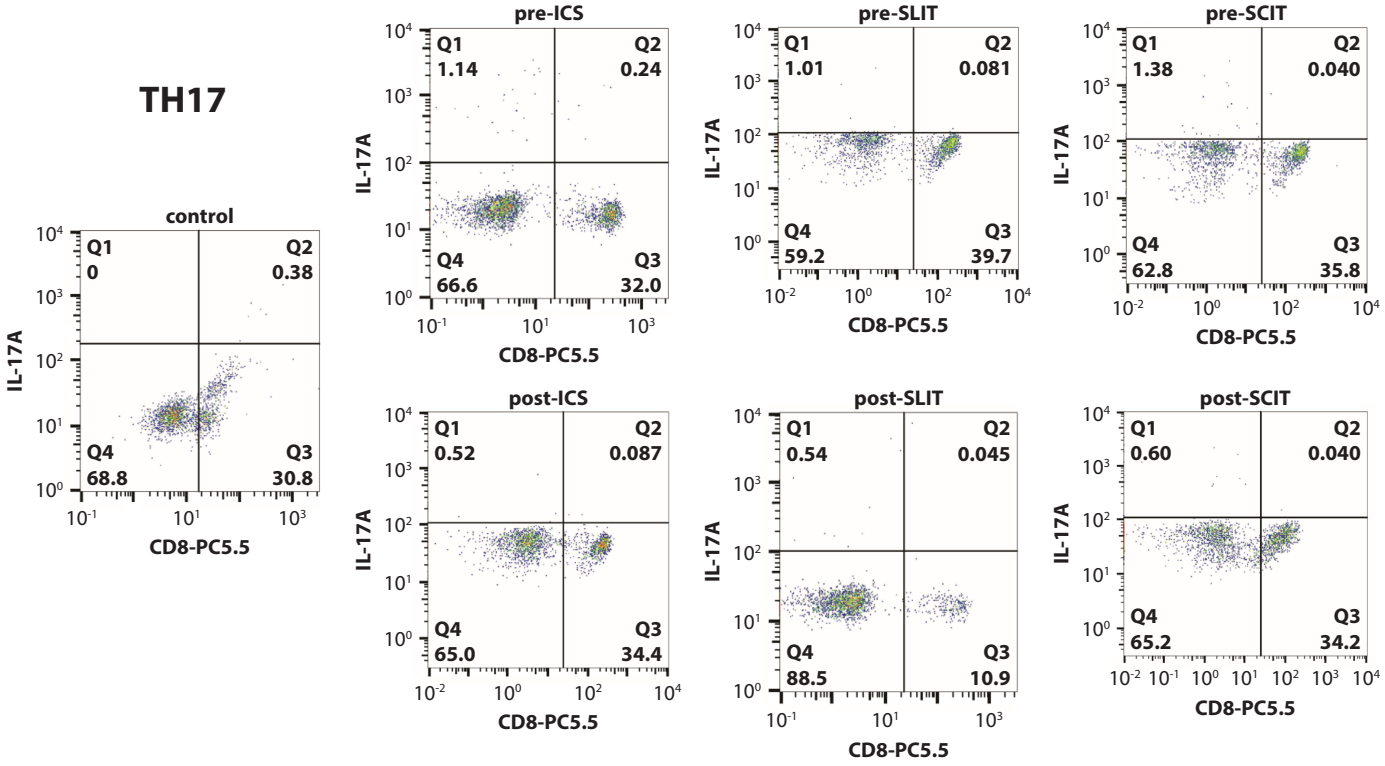

Figure 1. Flow cytometry plots of Th17 cells.

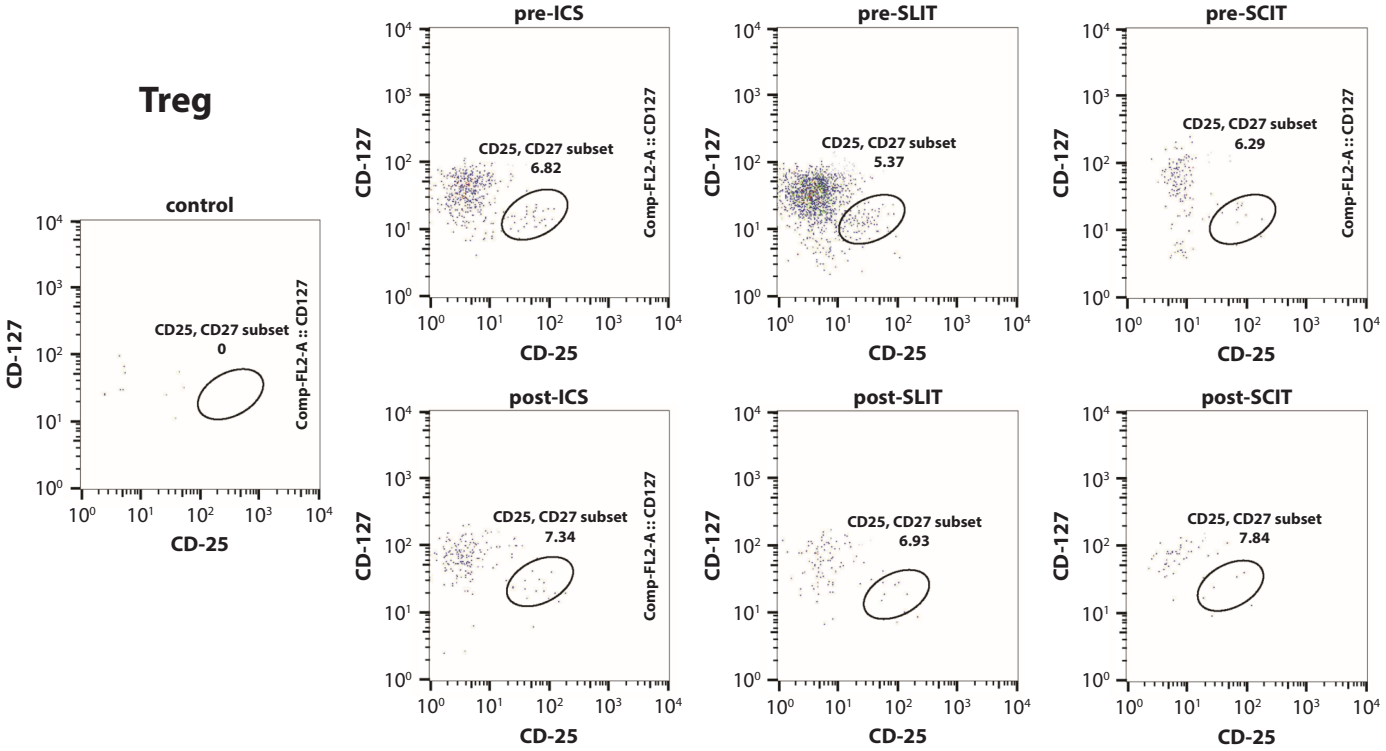

Figure 2. Flow cytometry plots of Treg cells.

Comparison of Treg, Th17, and Cytokine Levels Before and After Treatment

Due to non-normal distribution, the Kruskal–Wallis H test was used. No significant differences were found among the three groups for Treg, Th17, IL-17, IL-10, or IL-9 levels, either before or after treatment (all $p > 0.05$).

Within-group comparisons showed that all immune indices changed significantly pre- vs. post-treatment (all $p < 0.05$), except for Treg levels in the ICS group, which did not change significantly ($p > 0.05$). Specifically, Treg and IL-10 levels increased after treatment, whereas Th17, IL-17, and IL-9 levels decreased. Details are shown in **Table 3** and **Figure 1**, **Figure 2**.

Discussion

Pediatric asthma is characterized by chronic airway inflammation and hyperresponsiveness, making inflammation control and immune tolerance induction crucial for effective management.[8] While ICS are the cornerstone of treatment and effectively reduce airway inflammation and hyperreactivity, they do not modify the underlying immune imbalance caused by allergens and may lead to relapse after discontinuation.[9,10] SIT helps to establish long-term immune tolerance to allergens and has shown sustained clinical benefit even after cessation of therapy.[2,11,12] Both SCIT and SLIT immunotherapy have been proven effective in improving asthma symptoms and lung function, and are endorsed as adjunct therapies by GINA guidelines.[13,14] However, studies comparing their relative efficacy have yielded conflicting results. Some have suggested that SCIT is superior to SLIT in symptom control and pulmonary improvement.[13,15-18] Our findings support the superiority of SIT (SCIT or SLIT) combined with ICS over ICS monotherapy in improving asthma control and lung function. However, SCIT did not show a significant advantage over SLIT in this study.

Recent advances in immunology have highlighted the role of Th17 and Treg cells in the pathogenesis of asthma, offering a deeper understanding beyond the traditional Th1/Th2 imbalance. Recent advances in immunology have highlighted the role of Th17 and Treg cells in the pathogenesis of asthma, offering a deeper understanding beyond the traditional Th1/Th2 imbalance. In the presence of TGF-β alone, $CD4^+$ T cells differentiate into Treg cells, whereas in the presence of both TGF-β and IL-6, they differentiate into Th17 cells—two lineages with antagonistic roles. Th17 cells secrete pro-inflammatory cytokines such as IL-17, contributing to airway inflammation and asthma progression.[19] In contrast, Treg cells play a critical role in immune tolerance by suppressing Th2 and Th17 responses.[20] Moreover, IL-9, produced by Th9 cells under IL-4 and TGF-β stimulation, has emerged as a key cytokine in the pathogenesis of bronchial asthma.[21,22]

We further investigated changes in Th17 cells, Treg cells, and related cytokines. Although intergroup comparisons of Treg, Th17, IL-17, IL-9, and IL-10 levels before and after treatment did not reveal statistically significant differences, post-treatment Treg levels significantly increased in both the SCIT and SLIT groups, but not in the ICS group. This finding suggests that SCIT and SLIT may share similar mechanisms in inducing immune tolerance, likely associated with the proliferation of Treg cells.

Previous studies have demonstrated that Treg cells attenuate allergic responses by suppressing the activation and proliferation of effector T cells, thereby reducing the immune system's overreaction upon re-exposure to the same allergen in children with asthma. This mechanism contributes to the mitigation or prevention of asthma exacerbations. Additionally, Treg cells can modulate B cell function, inhibiting B cell activation and antibody production, particularly the secretion of allergen-specific IgE. This immunomodulation helps alleviate allergic inflammation and reduces the frequency and severity of asthma attacks.[14,23]

It is important to acknowledge several limitations of this study. First, the relatively small sample size and limited follow-up duration may reduce the generalizability of our findings. Second, this was a single-center study, which could introduce selection bias and limit external validity. Lastly, given the complex pathogenesis of asthma involving multiple immune cells and cytokines, future studies should include larger cohorts and explore additional immunologic pathways to better understand how SIT modulates immune responses in children with bronchial asthma.

Conclusion

This study demonstrates that SCIT or SLIT combined with ICS offers superior clinical efficacy compared to ICS monotherapy. SCIT and SLIT appear to share similar mechanisms of inducing immune tolerance, potentially mediated by the expansion of Treg cells.

Acknowledgments

Not applicable.

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

- JW and SW: concept/design, data collection, drafting article.
- CY: conduct experiments.
- XW and LZ: data collection.
- XJ: concept/design, data analysis/interpretation, critical revision of the article.

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Data Availability Statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

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