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Sublingual immunotherapy with *Dermatophagoides farinae* drops for pediatric atopic dermatitis

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Abstract

Background

We evaluated the clinical effect and safety of sublingual immunotherapy (SLIT) with *Dermatophagoides farinae* drops for pediatric atopic dermatitis (AD).

Methods

We enrolled children aged 4–13 years with AD and grouped them into the SLIT and control groups using the random number table method. We subdivided each group based on treatment duration (1-, 2-, and 3-year subgroups). The SLIT group received *Dermatophagoides farinae* drops, and both groups received conventional treatment (topical glucocorticoids, skin moisturizers, oral antihistamines, and allergen avoidance). Effective rate and effect were compared between groups after 1, 2, and 3 years of treatment.

Results

We assessed 309 SLIT cases (male, 192; age, 4–13 years) and 131 controls (male, 79; age 4–13 years). The effective rate and curative effect after 2 and 3 years of treatment were

significantly different between the groups ($P < 0.05$). The effect and effective rates between corresponding SLIT and control group treatment duration subgroups were significantly different ($P < 0.05$). SLIT group duration subgroups showed significant differences in the effect and effective rates ($P < 0.05$). Posttreatment Scoring Atopic Dermatitis (SCORAD) scores in the SLIT group duration subgroups were significantly lower than those of the corresponding control subgroups ($P < 0.05$). Upon follow-up at 1 year post treatment completion, the SLIT group's SCORAD score was significantly lower than its baseline score and the control group's follow-up score ($P < 0.05$).

Conclusion

SLIT with *Dermatophagoides farinae* drops for pediatric AD is safe and effective; effectiveness is maintained after treatment cessation, and prolonged treatment improves efficacy.

Introduction

With the current rapid development of industrialization and urbanization, more people develop allergic diseases including atopic dermatitis (AD), allergic rhinitis, and asthma. AD is a chronic, recurrent, inflammatory skin disease that has a high incidence rate in the pediatric group. Boguniewicz found that many factors influence the occurrence and development of AD.¹ Heredity, environment, skin barrier function, and psychologic factors all affect the disease.^{1, 2} Pediatric AD often causes severe pruritus, which adversely affects sleep and concentration. These effects may impact growth, development, and, in school-aged children, academic performance.

Although topical treatments and oral antihistamine treatments may lead to AD remission, the disease frequently relapses after drug withdrawal, making it difficult to achieve long-term remission.³ Dust mites and their secretions and excreta are highly allergenic,⁴ and dust mite allergens are ubiquitous and unavoidable; this is particularly true in regions with high humidity, such as coastlines, and tropical and subtropical areas. Allergic disease treatments consist of ensuring environmental hygiene in daily life, administering topical and oral symptomatic medications, and allergen-specific immunotherapy (ASIT). All these approaches are recommended treatments for dust mite allergy-related AD in children. However, only ASIT has the potential to change the natural course of allergic diseases.

ASIT, also known as desensitization therapy, has been used to reduce patient sensitivity to airborne allergens for over a century and has been widely used to treat allergic rhinoconjunctivitis and asthma.⁵ According to many clinical studies, ASIT achieves good results in patients with dust mite allergy-induced allergic rhinitis and asthma. Evidence-based research has confirmed that ASIT effects persist even after treatment cessation.⁶

Although ASIT's desensitizing mechanism has not been fully elucidated, researchers have

expanded our understanding of its actions in recent years.⁷ ASIT inhibits the early and late reactions to allergen exposure, resulting in an increased serum level of allergen-specific IgG4. Currently, IgG4 is considered a “blocking antibody,” which not only can block mast cell and basophil degranulation and release histamine caused by IgE cross-linking but can also block IgE-mediated antigen presentation.⁸ These blocking actions inhibit the generation of allergic symptoms and protect the body. Some studies also found that the average level of specific anti-dust mite IgG4 antibody in the serum of asthmatic children treated with ASIT increased as clinical symptoms improved.

Currently, there are two main ASIT methods: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). However, SLIT is chiefly used to treat asthma and allergic rhinitis, and few studies have evaluated its use for AD, especially in children. Therefore, we investigated the efficacy and safety of dust mite (*Dermatophagoides farinae*) drop SLIT for the treatment of children with dust mite allergy-related AD.

Materials and methods

We enrolled children aged 4–13 years diagnosed with AD in the outpatient Department of Dermatology, Pediatrics Hospital of Hunan Province from January 2014 to December 2018. Hunan Province, located in the middle of China, has a humid subtropical monsoon climate, with an annual average temperature of 16–19°C and a humidity of 60–89%. This is a randomized controlled trial wherein patients were grouped into the SLIT and control groups using the random number table method. Both groups received conventional therapy (oral antihistamines and topical glucocorticoids), and the SLIT group received additional sublingual *Dermatophagoides farinae* drops. Both groups were subgrouped based on the duration of treatment (1-, 2-, and 3-year subgroups). Informed consent was signed by the children’s legal guardians. The Pediatrics Hospital of Hunan Province Ethics Committee approved this study (#2013088), and it was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Enrollment

Our inclusion criteria were stable stage AD by Williams’ criteria for AD⁹; a positive dust mite skin prick result (+ + and above) or serum IgE ≥ 0.7 kUA/L (i.e., grade 2 and above); normal pretreatment vital signs; no participation in a drug clinical trial in the previous month; regular clinical and telephone follow-up evaluations; and no history of severe cardiovascular, immunodeficiency, or autoimmune disease or anaphylactic shock.⁹

Our exclusion criteria were acute infectious, systemic, or another autoimmune disease at the time of enrollment; oral administration of glucocorticoids or immunosuppressive drugs within the previous month; inability to cooperate with SLIT administration; a history of acute, severe asthma or hospitalization for asthma in the previous 3 months; a severe mental disorder on admission; simultaneous use of beta-blockers and ACE inhibitors; acute or

chronic cardiovascular dysfunction at the time of enrollment; and severe renal dysfunction.

Evaluations

During treatment appointments at our hospital, doctors carried out a meticulous physical examination and recorded symptoms and signs in detail. Doctors and parents completed the questionnaire survey, and parents signed the informed consent forms.

The dust mite skin prick test was considered positive⁹ in the presence of a wheal diameter ≥ 3 mm with surrounding skin erythema. We graded SLIT adverse reactions according to the American Society of Allergy, Asthma and Immunology Joint Working Group grading method³: (1) mild, local or systemic adverse reactions, and mild symptoms; (2) moderate, adverse reactions requiring timely treatment including drug treatment, dose adjustment, or discontinuation of immunotherapy; (3) severe, potentially fatal adverse reactions including asthma attacks and patients requiring hospitalization; and (4) anaphylactic shock. We used the Scoring Atopic Dermatitis (SCORAD) score¹⁰ to assess the lesion area (a), severity (b), and pruritus and sleep impact (c).

We evaluated the curative effect¹⁰ by calculating the improvement rate, as demonstrated in the following equation:

$$\text{Improvement rate} = [(\text{SCORAD score before treatment} - \text{SCORAD score after treatment}) / \text{SCORAD score before treatment}] \times 100\%.$$

An improvement rate $>95\%$ was considered cured; 61–95%, markedly improved; 20–60%, partially improved; $<20\%$, invalid. Additionally, the effective rate was calculated using the following equation:

$$\text{Effective rate} = [(\text{cured cases} + \text{markedly improved cases}) / \text{total cases}] \times 100\%.$$

A visual analog scale (VAS) score was used to evaluate the degree of itching and sleep disturbance; children under 6 years old answered with the help of their parents, and those over 6 years old answered by themselves.¹⁰ The children or their family members were selected according to the degree of symptoms.

Immunotherapy

The SLIT group received sublingual *Dermatophagoides farinae* drops produced by Zhejiang Iwu Biotechnology Co., Ltd. (Zhejiang Province, PRC; executive standard, ws4 - (s-012) - 2010z; approval number, State Medical Permitment No. S20060012). The preparation is a

colorless to a yellowish clear liquid, and the main components are normal saline and extract of dust mite metabolism. The drops are provided in 2 mL bottles in five protein concentration levels for adult maintenance treatment (number 1, 1 $\mu\text{g/mL}$; number 2, 10 $\mu\text{g/mL}$; number 3, 100 $\mu\text{g/mL}$; number 4, 333 $\mu\text{g/mL}$; number 5, 1000 $\mu\text{g/mL}$). During the first 3 weeks, we increased the concentration and dose according to a routine. Protein concentration number 1 was used in the first week, number 2 in the second, and number 3 in the third, each for 7 consecutive days; the daily dose increased per week as follows: 1, 2, 3, 4, 6, 8, and 10 drops. From the fourth week to the end of the treatment period, protein concentration number 4 (3 drops/d) was given as a maintenance dose. The drops were applied under the tongue, and the patient swallowed after approximately 2 minutes. The medicine was administered daily at a fixed time.¹⁰

Conventional treatment and follow-up

The SLIT and control groups received routine AD treatment including topical glucocorticoids, skin moisturizers, oral antihistamines, and allergen avoidance education. As sublingual placebo drops are never identical, and it is impossible to administer placebos alone for an extended period, we provided conventional treatment to the control group.

All subjects were evaluated at 2 months, 6 months, 1 year, 2 years, and 3 years after the first visit. The follow-up methods included outpatient appointments, telephone and WeChat interviews, SMS, QQ, and email exchanges.

Statistical methods

We analyzed data using SPSS v. 24.0 software (IBM Corp., Armonk, NY, USA). The Wilcoxon nonparametric rank-sum test was used for between-group comparisons. Comparisons between two independent samples were conducted using *t* tests. The chi-squared test was used to compare the effective rate between groups (Fig. 1).

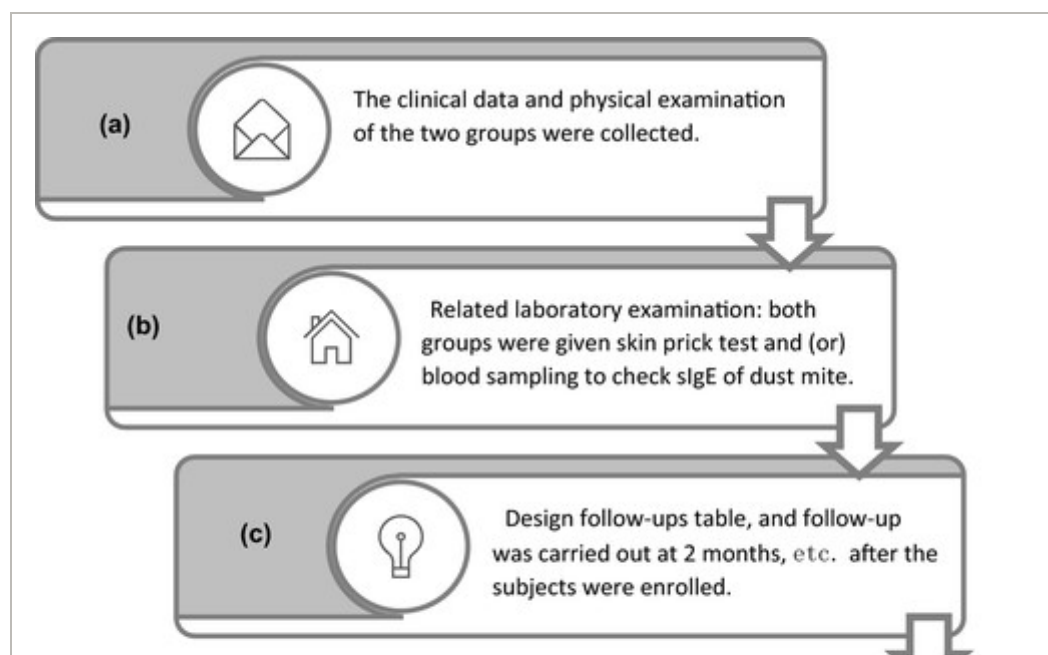




Figure 1

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Pediatric atopic dermatitis study flow diagram. (a) We collected clinical data and physical examination in the treatment and control groups. (b) Both groups underwent a skin prick test or blood sampling to assess dust mite sIgE. (c) We designed follow-up tables and performed follow-up 2 months, 6 months, 1 year, 2 years, and 3 years after enrollment. (d) We performed data analysis and comparisons

The treatment course of SLIT is generally 3–5 years. Cases wherein the treatment course was stopped for reasons other than improvement in the patient’s condition were regarded as lost to follow-up; these were included in the statistical analysis.

Results

Patient cohort

There were 309 patients in the SLIT group (male, 192 [62%]; female, 117 [37.9%]; age range, 4–13 years [average age, 7 years]; 1-year subgroup, 205 cases; 2-year subgroup, 77 cases; 3-year subgroup, 27 cases). On the other hand, there were 131 patients in the control group (male, 79 [60.3%]; female, 52 [39.7%]; age range, 4–13 years [average age, 6.6 years]; 1-year subgroup, 57 cases; 2-year subgroup, 38 cases; 3-year subgroup, 36 cases). There were no significant between-group differences in baseline patient characteristics ($P > 0.05$, Table 1). In the SLIT group, 69 (22.3%) patients had a family history of allergy, 70 had an sIgE level of 2–3 or a ++ *Dermatophagoides farinae* skin prick result, 239 had an sIgE level ≥ 4 or a ++ dust mite skin prick result, and 14 (4.5%) had asthma. There were 95 cases (30.7%) of rhinitis and 22 cases (7.1%) of comorbid allergic rhinitis and asthma. In the control group, 30 patients (22.9%) had a family history of allergy, 37 (28.2%) had an sIgE level of 2–3 or a ++ dust mite skin prick result, 94 (71.6%) had an sIgE level ≥ 4 or a ++ dust mite skin prick result, and three (2.3%) had asthma. There were 35 cases (26.7%) of rhinitis and six cases (4.6%) of comorbid allergic rhinitis and asthma (Table 1).

Table 1. Baseline characteristics in patients with pediatric AD: sublingual immunotherapy and control groups

	SLIT group (n = 309)	Control group (n = 131)	χ^2/Z	P
Sex				
Male (%)	192 (62.1)	79 (60.3)	0.130	0.718

	SLIT group (n = 309)	Control group (n = 131)	χ^2/Z	<i>P</i>
Female (%)	117 (37.9)	52 (39.7)		
Average age (years)	7 (5.75, 9.3)	6.6 (5.5, 8.8)	-0.693	0.488
Family history of allergy				
Yes (%)	69 (22.3)	30 (22.9)	0.017	0.896
None (%)	240 (77.7)	101 (77.1)		
Degree of dust mite allergy				
Prick ++/slgE 2-3 level	70 (22.7)	37 (28.2)	1.562	0.211
Prick+++ or ++++/slgE ≥ 4 level	239 (77.3)	94 (71.8)		
Comorbid respiratory and atopic disease				
Asthma (%)	14 (4.5)	3 (2.3)	-1.864	0.062
Allergic rhinitis (%)	95 (30.7)	35 (26.7)		
Rhinitis and asthma (%)	22 (7.1)	6 (4.6)		

SLIT, sublingual immunotherapy.

After treatment for more than 1 year, 59 patients stopped treatment for various reasons, with a loss rate of 19.1%. After treatment for more than 2 years, 36 patients stopped treatment, with a loss rate of 34.6%. The total loss rate of the study was 30.7%. Among them, 45 cases were lost due to low self-esteem as an effect of treatment, 18 cases due to parents' anxiety over drug side effects, 14 cases due to poor compliance to follow-up visits, three cases due to change in treatment method, and 15 cases due to personal reasons of the patients and their families that were unrelated to treatment.

Effect

The total effective rates in the SLIT and control groups were 61.1 and 29.4%, respectively, and the difference was significant ($P < 0.05$, Table 2). The total effectiveness rate was 61.1% in the SLIT group and 29.4% in the control group, which was also significantly different ($P < 0.05$, Table 2). Sixty-six cases were lost to follow-up (44 cases in the treatment group and 22 in the control group).

Table 2. Total effective rates in 2019 in two groups of patients with pediatric AD (n, %)

Group	SLIT group	Control group	Z	χ^2	<i>P</i>
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Group	SLIT group	Control group	Z	χ^2	P
A	265	109	-4.233 [*]	31.234 [*]	0.000
I	64	13			
II	98	19			
III	72	68			
IV	31	9			
V	162 (61.6)	32 (29.4)			
VI	103 (38.9)	77 (70.6)			
B	27	36	-1.965 [*]	4.590 ^{**}	0.049 (Pz)
I	7	2			0.032 (Px ²)
II	13	15			
III	2	16			
IV	5	3			
V	20 (74.1)	17 (47.2)			
VI	7 (25.9)	19 (52.8)			

A, Comparison of total effective rate; B, after **3** years of treatment; C, after **2** years of treatment; D, after **1** year of treatment.

I, recovery; II, remarkable effect; III, improved; IV, ineffective; V, recovery + marked effect; VI, improved + ineffective; SLIT, sublingual immunotherapy.

* Statistically significant *P* value (>0.05).

** Statistically significant *P* value (<0.05).

After 2 and 3 years of treatment, the effective rates were 51.0% and 74.1%, respectively, in the SLIT group and 31.1% and 47.2%, respectively, in the control group. The difference in the 2- and 3-year effective rates between the groups was statistically significant ($P < 0.05$). In contrast, the effective rates in the SLIT and control groups after only 1 year of treatment were 28.5% and 19.1%, respectively, which was not significantly different ($P > 0.05$, Table [2](#)).

There was no significant difference in baseline SCORAD score between the SLIT and the control groups ($P > 0.05$). The posttreatment SCORAD score in the SLIT group was lower than that of the control group, and the difference was statistically significant ($P < 0.05$, Table [3](#)).

Table 3. Comparison of Scoring Atopic Dermatitis scores between the treatment and control group treatment duration subgroups

Course	SLIT group	Control group	t/Z	P
A				
I	60 ± 9.038	57.75 ± 6.531	1.148	0.256
II	66 (50, 75)	62.19 ± 8.842	−1.679	0.093
III	65 (49, 74)	65.09 ± 8.998	−1.478	0.139
B				
I	20 (2, 24)	26.94 ± 13.657	−2.203	0.028
II	24 (18, 47)	32.43 ± 12.689	−1.966	0.049
III	33 (21, 52)	38.63 ± 13.218	−2.037	0.042
C				
G3	0 (0, 13)	27.74 ± 17.386	−3.984	0.000
G2	13 (4.25, 28.75)	31.5 (11.25, 37.50)	−2.747	0.006
G1	22 (5, 35)	34 (22, 44.25)	−2.621	0.009
D	A	C		
G3	60 (49, 64)	0 (0, 13)	−5.600	0.000
G2	71 (49.25, 75)	13 (4.25, 28.75)	−9.801	0.000

A, At baseline; B, after treatment; C, at follow-up in 2019; D, at baseline and at follow-up in 2019.

I, 3 years later; II, 2 years later; III, 1 year later.

G3, 3-year group; G2, 2-year group; G1, 1-year group; SLIT, sublingual immunotherapy.

The SCORAD score in each treatment group at 1 year post treatment completion was lower than the corresponding baseline SCORAD score, and the differences were statistically significant ($P < 0.05$, Table 3).

The SLIT group’s SCORAD score at 1 year post treatment completion for all groups was lower than that of the control group, and the difference was statistically significant ($P < 0.05$, Table 3).

No severe adverse reactions occurred in the SLIT or control group. The incidence of adverse

reactions in the SLIT group was 2.59%. In the SLIT group, 8/309 children had local adverse reactions, including mild lip swelling (four cases), numbness (three cases), and pruritus (one case). These events occurred in the increasing dose period and were mild, tolerable, and self-limited (Table 3).

Discussion

In this study of treatments for pediatric dust mite allergy-related AD, we found that the total effective rate in the group receiving SLIT with *Dermatophagoides farinae* drops was 61.1%, compared with 29.4% in our control group, demonstrating that SLIT was significantly more effective than conventional treatment alone. Our findings support those of Lee¹¹ and Gendelman,¹² who also showed that SLIT is effective for the treatment of children with AD. Children find SLIT easier to tolerate than SCIT because it can be administered at home, and it avoids the pain of repeated injections. Moreover, and of particular importance for school-age children, SLIT utilizes less time and energy on frequent hospital visits required for safe administration of SCIT.¹³ Additionally, SLIT has fewer adverse reactions than SCIT. Currently, no SLIT-related deaths have been reported in the international literature.¹⁴ No serious adverse reactions occurred in our SLIT group or control groups. There were no life-threatening adverse reactions or fatalities over 3 years, similar to the results of other clinical studies,^{11, 12, 14} suggesting that SLIT is safe for the treatment of pediatric AD.

We found that after 1 year of treatment, the SCORAD score of the SLIT group was significantly lower than that of the control group. However, the effective rate and effect in the two groups showed no significant difference. In patients treated for more than 2 years, the SCORAD score of the SLIT group was significantly lower than that of the control group, and the posttreatment SCORAD score, effect, and effective rate in the SLIT group were significantly different than those in the control group. Therefore, ensuring a full SLIT treatment course is vital to achieving the desired clinical effect, and it also suggests that SLIT adherence for 1 year can also help improve clinical symptoms. Currently, the recommended SLIT course is typically 3–5 years to achieve satisfactory clinical efficacy and reduce the recurrence rate of allergic diseases.¹³ Some studies found that the symptoms of adults and children with AD who were treated with SLIT improved, the daily drug score and visual analog score decreased, and the total effective rate was significantly higher than that of corresponding control groups; however, although patients with mild to moderate AD substantially benefitted from SLIT, patients with severe AD showed little improvement.¹⁴

Our study showed that SLIT could also benefit children with severe AD and suggested that the longer the course of treatment, the better the effect. These findings are similar to those of other research.¹⁴⁻¹⁶ We conducted a uniform follow-up of all patients who participated in the study at 1 year post treatment completion for all groups. At that time, we found that the SCORAD score of the SLIT group was significantly lower than that of the control group, and the SCORAD score of the SLIT group was significantly lower than that of its baseline score. Further, the total effective rate of the SLIT group (61.1%) was significantly higher than the

total effective rate of the control group (29.4%). The effective rates of the 1-, 2-, and 3-year SLIT subgroups in 2019 were 54.5, 69.1, and 90.5%, respectively, which were significantly higher than those of the corresponding control group subgroups.

Moreover, the corresponding treatment duration subgroups in the SLIT group and control groups and the treatment duration subgroups of the SLIT group also showed significant differences. To sum this up, SLIT can cause long-term remission, and the effect can be maintained after treatment cessation.¹⁴⁻¹⁶ It is important to adhere to an adequate treatment length to ensure a beneficial effect.

In conclusion, ASIT with *Dermatophagoides farinae* drops is safe and effective in children with AD, and the effect can be maintained after treatment cessation. The course of treatment should be at least a year, and the longer the course, the better the effect. The drops also have a good therapeutic effect for pediatric AD in children allergic to dust mites; this treatment can prevent allergic rhinitis and asthma to a certain extent.

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