

ORIGINAL ARTICLE

Sublingual immunotherapy may be effective in reducing house dust mite allergies in children with atopic dermatitis

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Abstract

Aim: We evaluated the efficacy of sublingual immunotherapy for children aged 5–17 years with atopic dermatitis who were allergic to house dust mites.**Methods:** This open-label, controlled, randomised trial from June 2015 to February 2018 comprised 60 subjects from a specialist allergy centre in South Korea. Half received sublingual immunotherapy for 12 months and the other half formed the control group. The subjects were evaluated using specialist scores and specific immunoglobulin and skin prick tests.**Results:** Sublingual immunotherapy significantly decreased the mean Scoring Atopic Dermatitis measurements in the sublingual group from baseline (30.2 ± 10.7) to 3 months (20.7 ± 8.5) and the effects persisted at 12 months (21.5 ± 12.4). However, the control group only showed a significant difference between baseline (30.4 ± 11.9) and 12 months (24.3 ± 10.2). The levels of *Dermatophagoides farina*-specific immunoglobulin G4 significantly increased in the treatment group from baseline (0.6 ± 0.5) to 12 months (1.0 ± 0.7), with no significant changes in the control group. New sensitisations to two or more allergens between baseline and 12 months were significantly lower in the sublingual group (21.4%) than controls (54.2%).**Conclusion:** Sublingual immunotherapy improved disease severity and prevented new sensitisations in children with atopic dermatitis who were allergic to dust mites.

KEYWORDS

atopic dermatitis, disease severity, house dust mite, sublingual immunotherapy

1 | INTRODUCTION

Atopic dermatitis is a chronic, relapsing inflammatory skin disease that is characterised by pruritic skin lesions.¹ It affects approximately 20% of children and 10% of adults.² The condition usually develops in early childhood and is the first step in the allergic march that precedes the development of respiratory allergic diseases, such as asthma and allergic rhinitis.³

The major mechanisms underlying the pathogenesis of atopic dermatitis are increased by T helper 2-mediated responses, including the release of interleukins 4, 5 and 13, the production of immunoglobulin (Ig) E, the recruitment of eosinophils and disruption of the epidermal barrier function.^{4,5} Although atopic dermatitis is a heterogeneous disease, 80% of patients with atopic dermatitis have the extrinsic type with IgE to specific allergens.⁶ House dust mites are major inhalant allergens that cause immediate and delayed allergic responses and lead

Abbreviations: Ig, immunoglobulin; IGA, investigator global assessment; SCORAD, scoring atopic dermatitis.

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to worsening atopic dermatitis.⁷ In addition, specific IgE antibodies to common inhalant allergens in children with atopic dermatitis are a major risk factor for initiating the atopic march.⁸

Atopic dermatitis is usually treated with topical and systemic anti-inflammatory, anti-pruritic and immunosuppressive agents. Allergen-specific immunotherapy is the only disease-modifying treatment option for patients with IgE-mediated asthma or allergic rhinitis.⁹ A few studies have indicated that house dust mite immunotherapy can be effective for selected patients with atopic dermatitis.^{10,11} A meta-analysis provided moderate evidence of allergen-specific immunotherapy efficacy in atopic dermatitis.¹² An international consensus, published in 2015, indicated that sublingual immunotherapy was a suitable alternative to subcutaneous immunotherapy for allergic rhino-conjunctivitis and asthma.¹³ It was shown to be as effective as subcutaneous immunotherapy, was associated with fewer and milder systemic adverse reactions and was easy to apply.¹³ This approach also increased compliance, especially among children.¹⁴ However, there have only been a few published studies on sublingual immunotherapy using house dust mites for children with atopic dermatitis.¹⁵

The aim of this study was to assess the safety and efficacy of sublingual immunotherapy for house dust mite allergies in children with atopic dermatitis and its subsequent effect on the development of new sensitivities to allergens.

2 | METHODS

2.1 | Study design

This was an open-label, controlled, randomised trial that did not use placebos and was conducted between June 2015 and February 2018. Children aged 5–17 years with atopic dermatitis were recruited from the Childhood Asthma Atopy Center at Asan Medical Center Children's Hospital in Seoul, South Korea. The children were randomly assigned to either the sublingual immunotherapy or control group for 12 months. Both groups received any other pharmacological treatment they needed. Randomisation was performed using [randomization.com](https://www.randomization.com) number-generating software (Gerard Dallal) by an independent research assistant who was not involved in this study. The randomisation tables were stratified by age, namely ≤ 7 versus ≥ 8 years. Permuted block randomisation with block sizes of 10 and 20, respectively, were used with a 1:1 allocation ratio for the sublingual immunotherapy and control groups. Regular visits for clinical evaluations were scheduled at 3, 6, 9 and 12 months. These included the Scoring Atopic Dermatitis (SCORAD) and Investigator Global Assessment (IGA) tools, plus a visual analogue scale, medication score and a safety assessment. In addition, the levels of total and specific IgE and IgG4 to house dust mites in sera and a skin prick test were measured at baseline and the final 12-month visit. The trial complied with the Declaration of Helsinki. The institutional review board of Asan Medical Centre approved the protocol, and written informed assent or consent was obtained from the participants or their legal guardians.

Key Notes

- This randomised trial evaluated the efficacy of sublingual immunotherapy for children aged 5–17 years with atopic dermatitis who were allergic to house dust mites.
- Sublingual immunotherapy significantly decreased the mean Scoring Atopic Dermatitis measurements from baseline to 3 months, and the effect had persisted at 12 months.
- New sensitisations to 2 or more allergens between baseline and 12 months were significantly lower in the sublingual group than the controls.

2.2 | Patients

We enrolled children aged 5–17 years of both sexes with a clinical history of chronic atopic dermatitis, without evidence of spontaneous improvement upon enrolment. They were all sensitised to *Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*. These had been diagnosed by a positive skin prick test or house dust mites-specific IgE (>0.7 kU/L) in serum. They all had a SCORAD result of 9–103. We excluded patients with persistent food allergies, severe systemic disorders that required immunosuppressants and malignancies.

2.3 | Treatment

The standard extract used for sublingual immunotherapy throughout the study was Staloral (Stallergenes Greer) which contains equal amounts of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. The allergen extracts were graded into 2 concentrations: 10 and 300 IR/ml. During the first 6 days, the patients took daily increasing doses in the form of 1–10 puffs of the 10 IR/ml extract. To reach the maintenance dose, 300 IR/ml concentration vials were started on day 7, reaching 8 puffs on day 11. Once the build-up phase was complete, all patients took 4 puffs sublingually daily for 12 months. The drops were held under the tongue for 2 min and then swallowed in accordance with the manufacturer's instructions. The children and parents were received education on how to use the treatment properly and additional written instructions and drug diary cards were distributed. The use of concomitant medications, such as moisturisers and topical and systemic drugs, was permitted in both groups, according to each patient's clinical evaluation.

2.4 | Diagnostic procedures

The serum levels of specific IgE and IgG4 antibodies to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* were measured by ImmunoCAP (Thermo Fisher Scientific). The cut-off value for specific IgE was ≥ 0.35 kU/L. The skin prick test

was performed with 12 common aeroallergens belonging to five groups (Allergopharma GmbH & Co KG). These were mites (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*), moulds (*Alternaria*), pollens (birch, alder, oak, mugwort, ragweed and grass mix), animal dander (cat and dog) and insects (cockroach). Histamine and saline were used as positive and negative controls, respectively. A positive skin prick test was defined as a mean wheal diameter that was ≥ 3 mm and larger than a positive control.

2.5 | Evaluation parameters

The severity of atopic dermatitis was evaluated according to the SCORAD, which was the primary outcome, and the IGA. The SCORAD consists of extent, intensity and subjective symptoms and can be graded from 0 to 103.¹⁶ The IGA is a 6-point scale, where 0 indicates a clear result with no inflammatory signs of atopic dermatitis and 5 indicates very severe disease with severe erythema and papulation or infiltration with oozing or crusting. A visual analogue scale, ranging from 0 for no symptoms at all, to 10 for very severe symptoms, was used to measure the burden of the atopic dermatitis symptoms. Any medication used during the study was recorded, and the total amount used every month for 1 year was calculated for each participant. Each dose of oral antihistamines or topical steroids were scored as 1 point if the potency ranking was VI or VII or 2 points if the potency ranking was V or less.¹⁰ The development of any asthma and allergic rhinitis was evaluated by a physician in both groups at the end of the study. Parents were instructed to record any local or systemic reactions on a side effects report card after each sublingual immunotherapy administration. The side effects were checked during each scheduled visit. Any allergic reactions to sublingual immunotherapy that were observed were recorded by the study clinicians according to the World Allergy Organization grading system¹⁴ for sublingual immunotherapy local adverse events.

2.6 | Statistical analysis

The data are presented as means and standard deviations. The sample size was calculated to detect a reduction of 23% or more in the SCORAD, with a 5% significance level and a power of 95%.^{16,17} We planned to randomise 30 patients per group, based on an expected dropout rate of 10. An intention-to-treat analysis was performed for the primary and secondary outcomes, using data from all participants. An additional per-protocol analysis was performed to calculate any new sensitisations and new onset of asthma or allergic rhinitis at the end of the study. Paired *t* tests or independent *t* tests were used to analyse laboratory data and continuous variable. For skewed data, the intergroup differences were analysed using the Mann-Whitney *U* test and the Wilcoxon test was used for intra-group comparisons. Categorical variables were analysed using the chi-square test and McNemar's test. All statistical tests were two-sided, and $p < 0.05$ were considered statistically significant. PASW Statistics for Windows, version 18.0 (SPSS Inc) was used for the statistical analyses.

3 | RESULTS

3.1 | Patients

We enrolled 60 patients (51.7% boys) with a mean age of 8.8 years, and there were 30 participants in the intention-to-treat sublingual immunotherapy group and 30 in the control group. Of these, 54 patients (90.0%) completed the study. One child who received sublingual immunotherapy and 5 controls, were excluded from the analysis due to loss of follow-up over the 12-month study period. Table 1 depicts the study population's demographics and baseline characteristics. There were no significant differences, at baseline, between the patients who completed and dropped out of the study (Table S1).

TABLE 1 Baseline characteristics and demographics of the enrolled participants

	Sublingual immunotherapy group (n = 30)	Control group (n = 30)	p value
Sex (male/female)	14/16	17/13	0.447
Age (years)	8.9 $\pm$ 3.4	8.6 $\pm$ 3.0	0.720
Onset of atopic dermatitis (years)	1.9 $\pm$ 2.3	2.1 $\pm$ 2.5	0.671
Duration of atopic dermatitis (years)	7.6 $\pm$ 3.6	6.9 $\pm$ 3.8	0.518
SCORAD, total	30.2 $\pm$ 10.7	30.4 $\pm$ 11.9	0.960
Allergic rhinitis	12 (40)	8 (26.7)	0.281
Asthma	4 (13.3)	4 (13.3)	0.542
slgE to <i>Dermatophagoides pteronyssinus</i> (kU/L)	31.3 $\pm$ 5.5	39.4 $\pm$ 6.6	0.342
slgE to <i>Dermatophagoides farina</i> (kU/L)	55.6 $\pm$ 7.3	61.3 $\pm$ 7.4	0.568

Note: Data are presented as numbers (%) or means and standard deviations unless otherwise specified.

Abbreviations: SCORAD, scoring atopic dermatitis; slgE, specific immunoglobulin E.

3.2 | Efficacy

Sublingual immunotherapy decreased the mean total SCORAD from baseline (30.2 ± 10.7) to 3 months (20.7 ± 8.5 , $p < 0.001$) and the effect persisted until 12 months (21.5 ± 12.4 , $p = 0.011$). However, the control group only showed significant mean SCORAD changes between baseline (30.4 ± 11.9) and 12 months (24.3 ± 10.2). Likewise, the change in objective SCORAD showed the same trend as total SCORAD in both the sublingual immunotherapy and control groups. However, the change in mean total SCORAD at each follow-up visit from baseline was not significantly different between the sublingual immunotherapy and control groups (data not shown).

In addition, sublingual immunotherapy decreased the mean IGA scores from baseline (2.5 ± 0.7) to 3 months (2.0 ± 0.8 , $p = 0.011$) and the effect persisted until 12 months (2.1 ± 0.8 , $p = 0.019$). However, there were no significant improvements from baseline to each follow-up visit in the control group. The mean medication scores were significantly decreased in the sublingual immunotherapy group at 3–12 months from baseline, while there was only a significant change in these scores in the control group between baseline and 9 and 12 months. The sublingual immunotherapy group only showed

significant changes in the visual analogue scale scores between baseline and 6 months, but no such changes were seen in the control group between baseline and any of the follow-up visits (data not shown).

The intergroup comparisons showed that the sublingual immunotherapy group had significantly lower mean total and objective SCORAD scores at 3 months and significantly lower mean IGA scores at months 3, 6 and 9 months than the control group (Table 2).

3.3 | Change in immunologic responses after sublingual immunotherapy

The mean levels of *Dermatophagoides farina*-specific IgG4 increased from baseline (0.6 ± 0.5 mg/L) to 12 months (1.0 ± 0.7 mg/L) in the sublingual immunotherapy group ($p = 0.012$). However, there was no significant change in these levels between baseline (0.5 ± 0.2 mg/L) and 12 months (0.6 ± 0.3 mg/L) in the control group. There was no significant change in *Dermatophagoides pteronyssinus*-specific IgG4 levels between baseline and 12 months in both the sublingual immunotherapy and control groups. The intergroup comparisons

TABLE 2 Scoring atopic dermatitis (SCORAD), investigator global assessment (IGA) and medication scores at baseline and follow-up visits

	Visit	Sublingual immunotherapy group (n = 29)		Control group (n = 25)		p^a value
		Mean $\pm$ SD	p^b value	Mean $\pm$ SD	p^b value	
SCORAD, total	Baseline	30.2 ± 10.7		30.4 ± 11.9		0.960
	Month 3	20.7 ± 8.5	<0.001	26.6 ± 10.4	0.099	0.021
	Month 6	22.0 ± 13.1	0.013	27.1 ± 13.7	0.453	0.175
	Month 9	21.8 ± 11.1	0.009	25.7 ± 10.0	0.071	0.192
	Month 12	21.5 ± 12.4	0.011	24.3 ± 10.2	0.026	0.386
SCORAD, objective	Baseline	22.7 ± 9.2		23.3 ± 9.5		0.791
	Month 3	14.6 ± 6.6	<0.001	20.9 ± 8.2	0.101	0.002
	Month 6	16.2 ± 10.8	0.022	20.9 ± 9.8	0.374	0.108
	Month 9	16.4 ± 8.1	0.010	19.5 ± 7.9	0.060	0.166
	Month 12	16.2 ± 9.8	0.015	19.3 ± 7.8	0.048	0.207
IGA	Baseline	2.5 ± 0.7		2.5 ± 0.8		0.859
	Month 3	2.0 ± 0.8	0.011	2.4 ± 0.8	0.672	0.048
	Month 6	1.8 ± 0.9	0.005	2.4 ± 0.8	0.490	0.006
	Month 9	1.9 ± 0.8	0.009	2.4 ± 0.7	0.381	0.024
	Month 12	2.1 ± 0.8	0.019	2.4 ± 0.8	0.338	0.140
Medication score	Baseline	39.1 ± 27.2		41.3 ± 39.2		0.286
	Month 3	26.3 ± 28.2	0.022	29.6 ± 26.6	0.154	0.935
	Month 6	16.2 ± 15.3	<0.001	25.5 ± 32.6	0.111	0.130
	Month 9	17.8 ± 14.1	<0.001	19.4 ± 18.4	0.001	0.572
	Month 12	21.2 ± 24.1	0.006	19.3 ± 21.9	0.003	0.686

Note: Data are presented as means and standard deviations unless otherwise specified.

^aIntergroup comparison.

^bIntragroup comparison (baseline versus each month).

showed that the mean levels of IgG4 specific to *Dermatophagoides farina* and *Dermatophagoides pteronyssinus* at 12 months in the sublingual immunotherapy group were significantly higher than in the control group (Table 3). There were no significant changes in the mean levels of specific IgE or the wheal size in response to *Dermatophagoides farina* and *Dermatophagoides pteronyssinus* between baseline and 12 months in both the sublingual immunotherapy and control groups (data not shown).

3.4 | New sensitisation and new asthma and allergic rhinitis after sublingual immunotherapy

After 12 months, the rate of new sensitisation to allergens other than house dust mites was not significantly different between the sublingual immunotherapy and control groups. However, the rate of new sensitisation to 2 or more allergens was lower in the sublingual immunotherapy group (6/28, 21.4%) than in the control group (13/24, 54.2%) ($p = 0.021$). We performed a subgroup analysis of participants with mono-sensitisation and poly-sensitisation to house dust mites. In the mono-sensitisation group, the rate of new sensitisation to allergens other than house dust mites was lower in the sublingual immunotherapy group (2/11, 18.2%) than in the control group (6/7, 85.7%) ($p = 0.015$). In the poly-sensitisation group, there was no significant difference in the rate of new sensitisation to allergens other than house dust mites between the sublingual immunotherapy and control groups (Table 4). The prevalence of new-onset allergic rhinitis at the end of the study was zero in the 17 participants in the sublingual immunotherapy group and 3/17 (17.6%) in the controls ($p = 0.07$). There were no participants with new-onset asthma in either the sublingual immunotherapy or control groups.

3.5 | Safety

Adverse events were reported by 9/29 (31.0%) patients in the sublingual immunotherapy group and none in the control group. Nine local reactions were reported: 8 cases of oropharyngeal itching

and 1 case of localised lip swelling. These reactions were classified as grade 1 according to the World Allergy Organization's grading system. They resolved spontaneously, and they did not require treatment or dose adjustments. There were no systemic adverse reactions or severe local reactions in the sublingual immunotherapy group throughout the study period.

4 | DISCUSSION

This was an open-label, controlled, randomised study that did not use placebos. It demonstrated that providing children with atopic dermatitis with sublingual immunotherapy for house dust mites led to significant improvements in terms of the severity of atopic dermatitis severity and medication requirements. Sublingual immunotherapy with house dust mites had a preventive effect against new sensitisations to two or more allergens. In addition, the preventive effect of sublingual immunotherapy against the development of new sensitisations was observed in participants with mono-sensitisation to house dust mites.

In our study, sublingual immunotherapy significantly decreased the mean SCORAD and IGA scores 3 months after baseline, and the effect persisted until the 12 months of treatment finished. Conversely, the control group only showed significant mean SCORAD changes between baseline and 12 months. Furthermore, intergroup comparisons found that mean SCORAD scores at 3 months, and the IGA scores at 3, 6 and 9 months were significantly lower in the sublingual immunotherapy group than in the control group. These results were consistent with previous studies, which reported that sublingual immunotherapy was effective at reducing the severity of atopic dermatitis in children.¹⁷⁻¹⁹ However, the changes in the mean total SCORAD scores at each follow-up visit from baseline were not significantly different between the 2 groups. These results may not provide sufficient high-quality evidence to demonstrate the efficacy of sublingual immunotherapy in children with atopic dermatitis. Most of the participants (95.0%) in our study had mild to moderate severity at enrolment and this means that the differences in outcomes from baseline to 12 months may have been

	Sublingual immunotherapy group (n = 29)	Control group (n = 25)	p value
<i>Dermatophagoides farina</i> -specific IgG4 (mg/L)			
Baseline	0.6 ± 0.5	0.5 ± 0.2	0.338
12 months	1.0 ± 0.7	0.6 ± 0.3	0.013
p^a value	0.012	0.552	
<i>Dermatophagoides pteronyssinus</i> -specific IgG4 (mg/L)			
Baseline	0.7 ± 0.5	0.6 ± 0.3	0.387
12 months	0.8 ± 0.5	0.6 ± 0.3	0.047
p^a value	0.329	0.925	

Note: Data are presented as means and standard deviations.

^aIntragroup comparison (baseline vs. 12 months).

TABLE 3 Changes in *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*-specific immunoglobulin G4 (IgG4) after 12 months

TABLE 4 New sensitisations that developed in the study groups

	Sublingual immunotherapy group	Control group	<i>p</i> value
Number at baseline	30	30	
Number at 1-year follow-up	28 (93.3)	24 (80.0)	
New sensitisations	16 (57.1)	19 (79.2)	0.091
1 new sensitisation	10 (35.7)	6 (25.0)	0.549
≥2 new sensitisations	6 (21.4)	13 (54.2)	0.021
Participants with mono-sensitisation to house dust mites at baseline			
New sensitisations	2/11 (18.2)	6/7 (85.7)	0.015
Participants with poly-sensitisation at baseline			
New sensitisations	14/17 (82.4)	13/17 (76.5)	0.676

Note: Data are presented as numbers (%).

too small to definitively evaluate improvements. Moreover, the severity of atopic dermatitis may have improved, at least in part, because of treatment, other than sublingual immunotherapy, that the subjects received during the study period. In addition, 12 months of sublingual immunotherapy may not have been enough to evaluate improvements in atopic dermatitis, as this was shorter than the duration of treatment in previous studies.^{17,18} One study has reported that the maximal clinical effect of allergen-specific immunotherapy with inhalant allergens was achieved within 1–2 years of treatment.²⁰ However, the lack of clinical trial data makes it difficult to reach definitive conclusions on the optimal duration of sublingual immunotherapy that is needed to evaluate improvements in children with atopic dermatitis.

In addition to clinical improvements after sublingual immunotherapy, we observed significant increases in house dust mite-specific IgG4 after 1 year of sublingual immunotherapy. This was similar to the findings of similar studies on children with allergic dermatitis.^{19,21} These changes in IgG4 support the efficacy of sublingual immunotherapy, based on the clinical outcomes of our study. However, our study did not meet all of the criteria for high-quality evidence, such as a double-blind approach and the use of placebos.

Previous studies have demonstrated that allergen-specific immunotherapy prevented the development of new sensitisations in patients who were already sensitised and had asthma and/or allergic rhinitis.^{22,23} In the present study, the preventive effect of sublingual immunotherapy was particularly evident in the development of new sensitisations to two or more allergens and in the participants with mono-sensitisation to house dust mites. The duration and route of allergen-specific immunotherapy may affect the degree of the preventive effect, which may lead to varying results among studies. We believe that this is the first report on the preventive effects of sublingual immunotherapy in terms of new sensitisations in children with atopic dermatitis. The mechanism underlying how sublingual immunotherapy prevents new sensitisations may be through immune tolerance, demonstrated by increased IgG4 or through by preventing epicutaneous sensitisation to other allergens by improved skin barrier function after sublingual immunotherapy. Further long-term

research is needed to evaluate the preventive effects of sublingual immunotherapy on the allergic march.

There were no life-threatening adverse events or severe local reactions during sublingual immunotherapy in the present study. The safety of this approach, even in children under the age of 5 years, has been demonstrated in several studies.^{24,25} Since the sublingual immunotherapy drops were administered at home, patients or caregivers should be carefully instructed, during regular follow-up sessions, about any side effects, how to manage the unexpected discontinuation of treatment, and situations that should be reported to their doctor. These instructions may increase treatment compliance and, thus, play a role in the therapeutic efficacy of sublingual immunotherapy.

The present study had some limitations. The major limitation was that it was conducted without double-blinding, because no placebo was available in our country. This may have affected the investigators' and participants' perceptions of outcomes. Other limitations were the single-centre study design and small sample size. The placebo effect cannot be isolated and properly assessed without a double-blind placebo-controlled trial. However, the placebo effect associated with sublingual immunotherapy (1.3%) has been reported to significantly lower than subcutaneous immunotherapy (40.5%).²⁶ Differences in the administration route may have resulted in differences in the magnitude of the placebo effect. Moreover, the increase of IgG4 levels after sublingual immunotherapy in our study may have been less affected by any placebo effect.

5 | CONCLUSION

This was an open-label, controlled, randomised study that did not use placebos. It suggests that sublingual immunotherapy may have reduced disease severity in children with atopic dermatitis who were allergic to house dust mites. It may also have prevented new sensitisations. Further studies are needed before the clinical application of sublingual immunotherapy is adopted for children with atopic dermatitis. Large-scale double-blind, placebo-controlled

design are needed, and these should cover other allergens as well as house dust mites.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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REFERENCES

- Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109-1122.
- Odiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. *J Allergy Clin Immunol*. 2009;124:1251-1258.e23.
- Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res*. 2011;3:67-73.
- Mansouri Y, Guttman-Yassky E. Immune pathways in atopic dermatitis, and definition of biomarkers through broad and targeted therapeutics. *J Clin Med*. 2015;4:858-873.
- Waldman AR, Ahluwalia J, Udkoff J, Borok JF, Eichenfield LF. Atopic dermatitis. *Pediatr Rev*. 2018;39:180-193.
- Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol*. 2003;112:252-262.
- Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J Allergy Clin Immunol*. 2006;118:1292-1298.
- Wuthrich B, Schmid-Grendelmeier P. Natural course of AEDS. *Allergy*. 2002;57:267-268.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1-S55.
- Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131:295.e1-299.e27.
- Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomised, dose-response study. *Allergy*. 2006;61:202-205.
- Bae JM, Choi YY, Park CO, Chung KY, Lee KH. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomised controlled trials. *J Allergy Clin Immunol*. 2013;132:110-117.
- Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568.
- Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7:6.
- Slavyanaka TA, Derkach VV, Sepiashvili RI. Debates in allergy medicine: specific immunotherapy efficiency in children with atopic dermatitis. *World Allergy Organ J*. 2016;9:15.
- Consensus Report of the European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology*. 1993;186:23-31.
- Di Rienzo V, Cadario G, Grieco T, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomised, open, parallel-group study. *Ann Allergy Asthma Immunol*. 2014;113:671-673.e1.
- Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomised, double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 2007;120:164-170.
- Sánchez Caraballo JM, Cardona VR. Clinical and immunological changes of immunotherapy in patients with atopic dermatitis: randomised controlled trial. *ISRN Allergy*. 2012;2012:183983.
- Penagos M, Durham SR. Duration of allergen immunotherapy for inhalant allergy. *Curr Opin Allergy Clin Immunol*. 2019;19:594-605.
- Qin YE, Mao JR, Sang YC, Li WX. Clinical efficacy and compliance of sublingual immunotherapy with *Dermatophagoides farinae* drops in patients with atopic dermatitis. *Int J Dermatol*. 2014;53:650-655.
- Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomised controlled study. *Ann Allergy Asthma Immunol*. 2008;101:206-211.
- Pajno G, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy*. 2001;31:1392-1397.
- Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol*. 2005;95:254-258.
- Rienzo VD, Minelli M, Musarra A, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy*. 2005;35:560-564.
- Narkus A, Lehnigk U, Haefner D, Klinger R, Pfaar O, Worm M. The placebo effect in allergen-specific immunotherapy trials. *Clin Transl Allergy*. 2013;3:42.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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