Original Article

Efficacy of House Dust Mite Sublingual Immunotherapy in Patients with Atopic Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Trial

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What is already known about this topic? The role of allergen immunotherapy in the management of patients with atopic dermatitis is considered controversial, and allergen immunotherapy is not recommended as a general treatment option for atopic dermatitis by current guidelines.

What does this article add to our knowledge? In this randomized, double-blind, placebo-controlled trial, sublingual immunotherapy with house dust mite extract showed efficacy in improving the signs and symptoms of atopic dermatitis in mite-sensitized patients after 18 months of treatment, as judged by SCORing Atopic Dermatitis tools, with no major adverse effects.

How does this study impact current management guidelines? Sublingual immunotherapy with house dust mite extract could be considered as a safe and effective add-on treatment for mite-sensitized patients with atopic dermatitis.

BACKGROUND: Sensitization to house dust mites (HDMs) is frequent in patients with atopic dermatitis.
OBJECTIVE: To investigate the efficacy of sublingual immunotherapy (SLIT) with *Dermatophagoides pteronyssinus* extract in patients with atopic dermatitis sensitized to HDM.
METHODS: In this randomized, double-blind, placebo-controlled trial, we enrolled 91 patients 3 years or older, with SCORing Atopic Dermatitis (SCORAD) score greater than or equal to 15 and positive skin test result and/or IgE to *D pteronyssinus*. Patients were stratified according to age (<12 and ≥12 years) to receive HDM SLIT or placebo for 18 months. Primary outcome was a greater than or equal to 15-point decrease in SCORAD score. Secondary outcomes were decreases in SCORAD and objective SCORAD, Eczema Area and Severity Index, visual analog scale for symptoms, and pruritus scale scores; Investigator's Global Assessment 0/1; and decrease greater than or equal to 4 points in Dermatology Life Quality Index. Background therapy was maintained.
RESULTS: A total of 66 patients completed the study (35 HDM SLIT, 31 placebo). After 18 months, 74.2% and 58% of patients in the HDM SLIT group and the placebo group, respectively, showed greater than or equal to 15-point decrease in SCORAD

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Abbreviations used
AD- atopic dermatitis
CrI- credible interval
DLQI- Dermatology Life Quality Index
Dpt- Dermatophagoides pteronyssinus
Der p 1- Dermatophagoides pteronyssinus allergen 1
Der p 2- Dermatophagoides pteronyssinus allergen 2
EASI- Eczema Area and Severity Index
HDM- house dust mite
IGA- Investigator's Global Assessment
IT- immunotherapy
MIC- minimal important change
SCORAD- SCORing Atopic Dermatitis
O-SCORAD- objective SCORing Atopic Dermatitis
SCIT- subcutaneous immunotherapy
SLIT- sublingual immunotherapy
VAS- visual analog scale

score (relative risk, 1.28; 95% CI, 0.89-1.83). Significant SCORAD score decreases from baseline of 55.6% and 34.5% in HDM SLIT and placebo groups (mean difference, 20.4; 95% CI, 3.89-37.3), significant objective SCORAD score decreases of 56.8% and 34.9% in HDM SLIT and placebo groups (mean difference, 21.3; 95% CI, 0.66-41.81), and more patients with Investigator's Global Assessment 0/1 in the HDM SLIT group as compared with the placebo group (14 of 35 vs 5 of 31; relative risk, 2.63; 95% CI, 1.09-6.39) were observed at 18 months.

CONCLUSIONS: Our results suggest that HDM SLIT may be effective in HDM-sensitized patients as an add-on treatment for atopic dermatitis. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Atopic dermatitis; House dust mite; Sublingual immunotherapy; Allergen immunotherapy; SCORing Atopic Dermatitis; Investigator's Global Assessment*

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and intense pruritus, which often has a profound impact on daily activities and quality of life of patients and their families.[1,2] Over the past few years, increased knowledge of the pathogenesis of AD has highlighted the central role of type 2 immune response, resulting in advances in treatment.[3-5] Therapeutic options for patients with AD that is not controlled with topical treatments are emerging, with safer profiles compared with those of traditional systemic treatments such as cyclosporine, methotrexate, long-term oral corticosteroids, and phototherapy.[3]

Therapies targeting type 2 immune responses include anti−IL-4/IL-13, anti−IL-13, and anti−IL-31 biologics.[3-5] Dupilumab, a fully human mAb directed to the alpha chain of the IL-4 receptor that prevents signaling by both IL-4 and IL-13, is the only biologic approved for use in children aged 6 to 12 years, adolescents, and adults with moderate to severe AD, showing efficacy and a favorable safety profile.[6-9] In addition to biologics, Janus-kinase inhibitors administered orally have demonstrated rapid onset of action and sustained decrease in signs and symptoms of AD.[10] This group of drugs prevents intracellular signaling through Janus-kinase/signal transducer and activator of transcription pathways in a broader capacity, including, but not limited to, the inhibition of downstream effects triggered by several cytokines involved in the pathogenesis of AD such as IL-4, IL-5, IL-13, IL-22, IL-24, and IL-31.[10] In a recent comparative study, dupilumab and the Janus-kinase inhibitor abrocitinib were both associated with reductions in signs and symptoms of AD as compared with placebo. Abrocitinib was superior to dupilumab in reducing itching at 2 weeks; however, the 2 drugs had similar outcomes.[11] Another recent randomized clinical trial showed that upadacitinib provided superior and more rapid skin clearance and itch relief compared with dupilumab in adult patients with moderate to severe AD.[12] Further information on the long-term efficacy and safety of Janus-kinase inhibitors in the treatment of AD will be provided by ongoing trials.[3]

Although new systemic therapies may achieve higher efficacy outcomes and drastically change patients' lives, their potential to modify the natural history of AD is not yet clear.[13] Moreover, the high cost of these drugs may limit their long-term use.[14] The early steps in the pathogenesis of AD include stimulation of keratinocytes, innate and adaptive immune cells by allergens, irritant substances, microorganisms, and mechanical damage from itching/scratching, within the context of a defective skin barrier, leading to a predominant type 2 immune response in most patients.[1,2] However, additional disease endotypes with the contribution from T_H17, T_H22, T_H1, IL-33, and IL-9 signatures have also been described in different age groups.[15-17] Sensitization to house dust mite (HDM) and food allergens is frequent among patients with AD; however, the role of IgE sensitization in the clinical course of AD is unclear.[18]

Allergen immunotherapy (IT) has been considered an effective, precision medicine treatment for IgE-mediated diseases including mild to moderate asthma, allergic rhinitis and conjunctivitis, anaphylaxis to Hymenoptera insect venom, and food allergy, and this therapy has been used for more than 100 years.[19] Subcutaneous immunotherapy (SCIT) has shown the potential to provide long-term disease control, even after treatment completion.[19] Over the past 30 years, sublingual immunotherapy (SLIT) has been introduced in allergy practice, with an efficacy comparable to that of SCIT, but with a safer profile allowing for unsupervised administration by the patient.[19,20] In a randomized, double-blind, placebo-controlled study performed in Germany, SCIT with mite extract was effective as an add-on therapy in adult patients with HDM sensitization and severe AD.[21] Few controlled studies have addressed the efficacy of SLIT in AD,[22,23] and its use in the treatment of AD is currently considered investigational or under debate.[20,24] The present study aimed to investigate the role of SLIT as an add-on treatment for patients with AD sensitized to HDM by performing a randomized, double-blind, placebo-controlled, 18-month clinical trial with HDM extract or placebo.

METHODS

Study design

This randomized, double-blind, placebo-controlled trial was conducted between May 2018 and June 2020 at the Clinical Research Unit of Ribeirão Preto Medical School Hospital, University of São Paulo, Brazil. The enrolled patients received house dust mite sublingual immunotherapy (HDM SLIT) or placebo 3 days a week for 18 months. Background therapy for AD was maintained according to the

current guidelines and experts' recommendations[2,3,18]; however, the treatment was individualized for each patient. During the trial, topical corticosteroids, topical immunosuppressors, and systemic immunosuppressants were administered. Oral corticosteroids were used only in short courses as rescue therapy for severe exacerbations. Treatment with omalizumab was allowed in patients who had received omalizumab previously. The use of dupilumab or indication for the use of dupilumab by the attending physician during the enrollment period was the exclusion criterion.

Patients

Patients 3 years or older diagnosed with AD according to the criteria of Hanifin and Rajka,[25] with SCORing Atopic Dermatitis (SCORAD)[26] score greater than or equal to 15 points, and sensitized to HDM *Dermatophagoides pteronyssinus* (Dpt) by skin prick test and/or specific IgE to Dpt measured using ImmunoCAP, were eligible for inclusion in the present study. The exclusion criteria were pregnancy or breast-feeding, use of immunosuppressants to treat inflammatory diseases other than asthma and AD, use of dupilumab to treat severe AD, interruption of HDM SLIT/placebo treatment for more than 8 weeks, increase in SCORAD 50% or greater from baseline, and severe allergic reactions to HDM SLIT/placebo that delayed progression within the study protocol. Patients were selected from among those who attended the Allergy and Immunology and Dermatology Clinics of Ribeirão Preto Medical School Hospital. Recruitment was also conducted by announcements on social media, paper leaflets, and posters. The recruitment period was 6 months.

Randomization and blinding

Patients were randomly allocated to treatment or placebo by block randomization (blocks of random size 4 or 6) and stratified according to age (<12 years or ≥12 years) using a previously generated randomization list made in sealed envelopes[27] and implemented in the REDCap platform.[28,29] The randomization list was generated by a researcher who was not involved in any interaction with the participants. The trial pharmacists performed the randomization process, and were blinded to the information on whether the patient belonged to the HDM SLIT group or the placebo group. The senior manager of the company who provided the Dpt extract for HDM SLIT and placebo (IPI-ASAC Brasil) held the secret code for each group (A and B) until the end of the trial. The laboratory personnel from IPI-ASAC Brasil prepared and provided identical vials with extract and placebo every 2 months, and labeled them by group. The pharmacists were responsible for the storage and delivery of the vials to the patients. Vials were labeled only with technical information, including the expiration date, concentration, batch, and bottle number. The researchers had no access to information on the patients' groups throughout the entire study period and up to the completion of the analysis of outcome measures.

Treatment with HDM SLIT and placebo

The treatment regimen comprised 3 doses per week of Dpt extract or placebo delivered by the sublingual route, followed by a 2-minute holding period and subsequent swallowing. The Dpt extract used in the present trial was provided by the laboratory IPI-ASAC Brasil, licensed in Brazil to prepare and commercialize the SLIT material from a lyophilized Dpt extract produced in Spain by ASAC Pharma. Measurement of major allergens in the extract using ELISA[30] revealed *Dermatophagoides pteronyssinus* allergen 1 (Der p 1) and *Dermatophagoides pteronyssinus* allergen 2 (Der p 2) levels of 6.7 μg/mL and 0.9 μg/mL, respectively (Der p 1 + Der p 2 of 7.6 μg/mL). Dilutions were prepared with double-distilled water containing 50% glycerol, with a maintenance dose of 8 drops of 1:10 volume:volume (v:v) dilution, which is equivalent to 0.3 μg of Der p 1 + Der p 2 allergens.

The induction phase started with an initial dilution of 1:1,000,000 v:v, progressing to 1:100,000 v:v, 1:10,000 v:v, 1:1000 v:v, 1:100 v:v, and 1:10 v:v dilutions of the extract, administered in escalating doses of 1, 2, 4, 6, and 8 drops for a period of 15 days for each vial with a new dilution. A maintenance dose of 8 drops of 1:10 v:v dilution of the extract was achieved after 3 months. The placebo solution was identical to the diluent of the extract, comprising double-distilled water and 50% glycerol, and the schedule of placebo administration was the same as that of HDM SLIT.

Clinical assessment

All patients underwent clinical assessments at baseline and after 3, 6, 9, 12, 15, and 18 months of treatment. Clinical assessment included SCORAD, objective SCORAD (O-SCORAD), Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Dermatology Life Quality Index (DLQI), visual analog scale (VAS) for symptoms, and pruritus score.[26,31-34] Clinical evaluation was performed by the same investigator throughout the study period. Patients had unrestricted access to communication with the investigator (S.S.L.) regarding adverse events and other issues using messaging applications.

Laboratory tests

Total IgE levels were measured at the clinical laboratory of the hospital using ImmunoCAP (Thermo Fisher Scientific, São Paulo, SP, Brazil) and expressed in IU/mL. Specific IgE was assessed at the beginning of the study using Immunosorbent Allergen Chip (Thermo Fisher Scientific), and the results were expressed in Immunosorbent Allergen Chip standardized units according to the manufacturer's instructions. The levels of Der p 1 and Der p 2 in the Dpt extract were measured in our research laboratory using ELISA.[30] Skin swabs from the affected areas were collected before the start of treatment and at the end of the study. Swab culturing was performed at the Microbiology Laboratory of the hospital, and *Staphylococcus aureus* was identified using the Vitek 2 Compact system (BioMerièux Itapevi, SP, Brazil).

Primary outcome

The meaningful within-subject response was set as a greater than or equal to 15-point decrease in SCORAD score, for any degree of severity, after 18 months of treatment.

Secondary outcomes

Any reduction in SCORAD, O-SCORAD, EASI, VAS, and pruritus score, in the percentage of patients who achieved improvement of at least 50% in EASI score from baseline, improvement of at least 75% in EASI score from baseline, and improvement of at least 90% in EASI score from baseline, proportion of patients who achieved IGA scores of 0 and 1, and a decrease of 4 or more points in the DLQI were the secondary outcome measures evaluated in the present study.

Ethical aspects

The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The Ethics Committee of Ribeirão Preto Medical School Hospital approved this study (protocol no. 2101981), and the trial was registered in the ClinicalTrials.gov

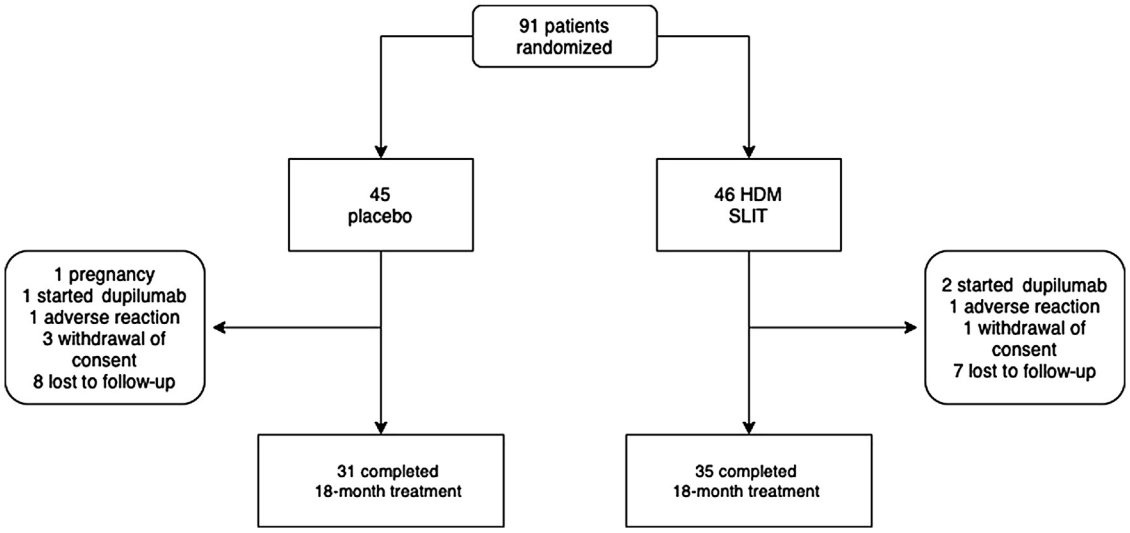

FIGURE 1. Study outline. Of the 91 patients enrolled in the study, 66 completed the 18-month treatment, including 35 patients in the HDM SLIT group and 31 patients in the placebo group.

(NCT 03388866). An independent investigator (C.E.S.G.) monitored patient safety. Assent and written informed consent were signed by each patient and, when appropriate, by parents or legal guardians.

Sample size calculation

The sample size was obtained considering a 5% significance level and power of 80% for a treatment response rate defined as a decrease of at least 15 points in the SCORAD after 18 months of treatment, assuming that 40% of the patients in the HDM SLIT group and 15% in the placebo group would achieve the proposed rate. Statistical calculations predicted that we would need 94 patients (47 patients in each group) to detect a significant difference between the 2 groups.[35]

Statistical analysis

After a detailed exploratory analysis and considering SCORAD, O-SCORAD, EASI, DLQI, VAS for symptoms, and pruritus scale in % of change from baseline, we compared groups at each time point by fitting Bayesian mixed regression models. Analysis was performed for complete cases, comprising patients who completed the 18-month treatment period; these patients had a full set of data on all clinical visits, at 3, 6, 9, 12, 15, and 18 months of follow-up (no missing data). We considered noninformative prior distributions, estimated mean differences, and 95% credible intervals (CrIs). Relative risks (RRs) and 95% CIs were obtained to compare the proportion of patients who reached improvement of at least 50% in EASI score from baseline, improvement of at least 75% in EASI score from baseline, and improvement of at least 90% in EASI score from baseline, IGA 0/1 and IGA 0/1 plus 2 or more points drop from baseline, and a decrease of 4 or more points in DLQI, adjusting log-binomial regression models. In all models, we inserted age ($<$12 years and $\geq$12 years) as a covariate, considering the stratification. For the statistical analysis, we used the library *R2jags* of R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and PROC GENMOD of SAS 9.4 (SAS Institute, Cary, NC) software.[36]

RESULTS

Characteristics of the patients participating in the study

Ninety-one patients were enrolled in the study, and 66 patients completed the 18-month treatment. Of these, 35 received HDM SLIT and 31 received placebo (Figure 1). Table I presents the demographic characteristics of the 66 patients who completed the study. Most patients presented with moderate and severe disease, as assessed by SCORAD and O-SCORAD. A high proportion of our patients had associated allergic conditions, including rhinitis, asthma, and keratoconjunctivitis. The IgE sensitization profiles of the patients in the placebo and HDM SLIT groups are presented in Figure 2, *A* and *B*, respectively, and Table E1 in this article's Online Repository at www.jaci-inpractice.org. Approximately one-third of our patients presented with culture-proven *S aureus* colonization. Short courses of oral corticosteroids as rescue therapy for severe exacerbations were used in only 3 patients in each group throughout the study (Table I).

After enrollment, 6 patients met the exclusion criteria and 4 withdrew their consent. Fifteen patients were lost to follow-up, mainly due to being unable to afford the costs of attending clinical visits (no financial compensation was available in the study to cover these expenses), moving to distant areas, inconvenient appointment times, or being unable to afford missing work (Figure 1). Overall, 17 of 25 (68%) patients terminated their participation in the study within the first 6 months.

Efficacy of HDM SLIT in patients with AD

At baseline, the mean SCORAD was 46.9 (range, 17-87). After 18 months, 74.2% and 58% of patients in the HDM SLIT group and the placebo group, respectively, achieved the primary outcome of a greater than or equal to 15-point decrease in the SCORAD score; however, this difference was not significant (RR, 1.28; 95% CI, 0.89-1.83). Significant SCORAD score decreases from baseline of 55.6% and 34.5% were present in the HDM SLIT group and in the placebo group, respectively, at 18 months, with a mean difference of 20.4 (95% CrI, 3.89-37.3; in

TABLE I. Demographic and clinical characteristics of patients with AD by treatment group

Characteristic	HDM SLIT (n = 35)	Placebo (n = 31)
Age (y), mean (range)	18.1 (5-62)	21 (3-58)
Age distribution		
<12 y	14 (40)	11 (35.5)
12 y and above	21 (60)	20 (64.5)
Sex		
Male	10 (28.6)	9 (29)
Female	25 (71.4)	22 (71)
SCORAD score, mean (range)	48.1 (28-87)	45.7 (17-85)
Mild (≤25)	0	2 (6.5)
Moderate (26-50)	19 (54.3)	17 (54.8)
Severe (51-103)	16 (45.7)	12 (38.7)
O-SCORAD score		
Mild (≤15)	0	3 (9.7)
Moderate (16-40)	23 (65.7)	19 (61.3)
Severe (41-83)	12 (34.3)	9 (29)
EASI, mean (range)	12.4 (2-41)	14.2 (0-51)
IGA score, mean		
0-1	4 (11.4)	3 (9.7)
2-3	28 (80)	23 (74.2)
4-5	3 (8.6)	5 (16.1)
DLQI, mean (range)	10.8 (1-24)	11.7 (5-24)
Total IgE (UI/mL), geometric mean (range)	2120 (46.8-34,980)	1507 (14.2-44,160)
IgE to Der p 1 (ISU-E*), mean (range)	37.9 (0-106.1)	29.3 (0-101.8)
IgE to Der p 2 (ISU-E*), mean (range)	44.9 (0-131.5)	48 (0-147.7)
Comorbidities		
Rhinitis	29 (82.9)	25 (80.6)
Asthma	17 (48.6)	13 (41.9)
Atopic keratoconjunctivitis	7 (20)	4 (12.9)
Food allergy	1 (2.9)	4 (12.9)
Urticaria	0	1 (3.2)
Contact dermatitis	12 (34.3)	8 (25.8)
Drug hypersensitivity	1 (2.9)	2 (6.5)
Molluscum contagiosum	0	1 (3.2)
Diabetes	0	1 (3.2)
Oral immunosuppressants†		
Cyclosporine		
Baseline	3 (8.6)	4 (12.9)
Within the 18-mo treatment	3 (8.6)	1 (3.2)
Methotrexate		
Baseline (%)	0	1 (3.2)
Within the 18-mo treatment (%)	0	4 (12.9)
Corticosteroid, long-term		
Baseline	1 (2.9)	0
Within the 18-mo treatment	0	0
Azathioprine		
Baseline	0	0
Within the 18-mo treatment	0	1 (3.2)
Short courses of oral corticosteroid within the 18-mo treatment‡	3 (8.6)	3 (9.7)
Anti-IgE therapy with omalizumab	0	2 (6.5)
Presence of *S aureus*—positive swab on skin lesions		
Baseline	12 of 35 (34.3%)	14 of 30 (46.7%)
After 18-mo treatment	10 of 35 (28.6%)	13 of 31 (41.9%)

(continued)

TABLE I. *(Continued)*

Characteristic	HDM SLIT (n = 35)	Placebo (n = 31)
Skin infections requiring antibiotics		
Oral antibiotics	16 of 35 (45.7%)	19 of 31 (61.3%)
	36 episodes	33 episodes
Parenteral antibiotics	0	3 of 31 (9.7%)
		3 episodes§

ISAC, Immunosorbent Allergen Chip; *ISU-E*, ISAC Standardized Units for IgE.
Values are n (%) unless otherwise indicated.
*Measurements ≥15 ISU-E considered as Very High, according to the manufacturer.
†During the study period, background treatment with topical corticosteroids and/or topical calcineurin inhibitors was maintained in all patients, in addition to skin moisturizers and emollients. During the trial, 14 patients (21.2%) used systemic immunosuppressants. Ten patients were using these medications at baseline; of these, 5 patients maintained the immunosuppressant (cyclosporin, 2 patients in the HDM SLIT group and 1 in the placebo group; methotrexate, 2 patients in the placebo group); 1 patient was switched from cyclosporin to methotrexate; and 4 patients were able to discontinue the immunosuppressant (cyclosporin, 1 patient in the HDM SLIT group and 2 in the placebo group; oral corticosteroid, 1 patient in the HDM SLIT group). Four patients were newly prescribed immunosuppressants (cyclosporin, 1 patient in the HDM SLIT; azathioprine, 1 patient in the HDM SLIT group; and methotrexate, 2 patients in the placebo group). Groups were too small to allow for statistical comparison.
‡Including oral corticosteroids prescribed by a family physician or pediatrician, or taken as self-medication, which is possible in Brazil.
§Including 1 patient admitted to the hospital who was treated with intravenous antibiotics.

this analysis, the result is statistically significant if the 95% CrI excludes 0) (Figure 3). The effect size was calculated according to Cohen[37] as $d = 0.59$, considered a medium effect size. Similarly, O-SCORAD score decreases from baseline of 56.8% and 34.9% were present in the HDM SLIT group and the placebo group, respectively, at 18 months, with a significant difference of 21.3 (95% CrI, 0.66-41.81; in this analysis, the result is statistically significant if the 95% CrI excludes 0) (Figure 4). Significantly more patients in the HDM SLIT group had an IGA 0/1 at 18 months than those in the placebo group (14 of 35 HDM SLIT and 5 of 31 placebo; RR, 2.63; 95% CI, 1.09-6.39; in this analysis, the result is statistically significant if the 95% CI excludes 1) (Figure 5, *A*). More patients in the HDM SLIT group had an IGA 0/1 plus a reduction from baseline of 2 or more points at 18 months as compared with those in the placebo group (6 of 35 HDM SLIT and 1 of 31 placebo); however, this difference was not significant (RR, 2.14; 95% CI, 0.34-13.69) (Figure 5, *B*). The proportion of patients who achieved a decrease of 4 or more points in the DLQI at 18 months was 68.5% and 80.6% for the HDM SLIT group and the placebo group, respectively (RR, 0.87; 95% CI, 0.65-1.16, not significant). No significant changes were found for EASI and DLQI scores, VAS scores for symptoms, and pruritus scores (see this article's Online Repository text and Figures E1, E2, and E3 at www.jaci-inpractice.org). Clinical photographs of a representative patient at baseline and after 18 months of HDM SLIT are shown in Figure 6.

Adverse events

The adverse events are described in Table II and in this article's Online Repository text and Figure E4 at www.jaci-inpractice.org. The most commonly reported adverse events were headache and abdominal pain, present in both the HDM SLIT and placebo groups. Some adverse events during the HDM SLIT treatment are shown in Figure E4.

DISCUSSION

We report the results of a randomized, double-blind, placebo-controlled clinical trial that investigated the efficacy of HDM SLIT in patients with AD while maintaining background therapy. After 18 months of treatment, significantly more patients in the HDM SLIT group presented an IGA 0/1 (clear or almost clear skin) and showed a significant reduction in SCORAD and O-SCORAD scores as compared with those in the placebo group. Although 74.2% and 58% of patients in the HDM SLIT group and the placebo group, respectively, achieved the primary outcome of reduction of 15 points or more in the SCORAD score, this difference was not significant, indicating a large placebo effect. In addition, no significant differences were observed in the patients' EASI, DLQI, VAS for symptoms, or pruritus scores. HDM SLIT was well tolerated, and no severe systemic reactions were observed. The most common adverse events were headache and abdominal pain, reported by patients in both the treatment and placebo groups.

SLIT has been established in clinical practice for the past 30 years.[20] For some patients, particularly children, SLIT could offer some advantages over traditional SCIT, including easier at-home administration, except for the first dose, which should be administered by the clinician under medical supervision, accompanied by a 30-minute observation period, a more favorable safety profile, a lower risk of serious systemic allergic reactions, and avoidance of needle phobia.[19,20] Currently, SLIT may be administered in 2 formulations as tablets (compressed or freeze-dried) that completely dissolve under the tongue, and as liquid drops.[38] Only SLIT tablet products are approved by the Food and Drug Administration in the United States. In the United States, SLIT administered as liquid drops is carried out by off-label use of SCIT extracts.[38,39] SLIT tablet products are limited to a single allergen; this is considered a barrier to SLIT use by some allergists in the United States.[39] Moreover, SLIT drops would offer the possibility to treat multiple allergen sensitivities at the same time and to use escalating doses, as is done with SCIT. There is no induction period in North America or Europe for approved SLIT products. Because of rare reports of anaphylaxis during SLIT, there is a black-box recommendation to prescribe autoinjectable epinephrine along with any SLIT tablet products in the United States. Currently, HDM SLIT tablets are approved for use only in adults aged 18 to 65 years by the Food and Drug Administration.[39] In the present study, the enrolled patients had high levels of total and specific IgE to HDM allergens and were possibly exposed to high levels of mite allergens in their homes based on our previous observations,[40] which could pose a risk for adverse reactions including worsening of skin lesions with treatment. The use of SLIT drops

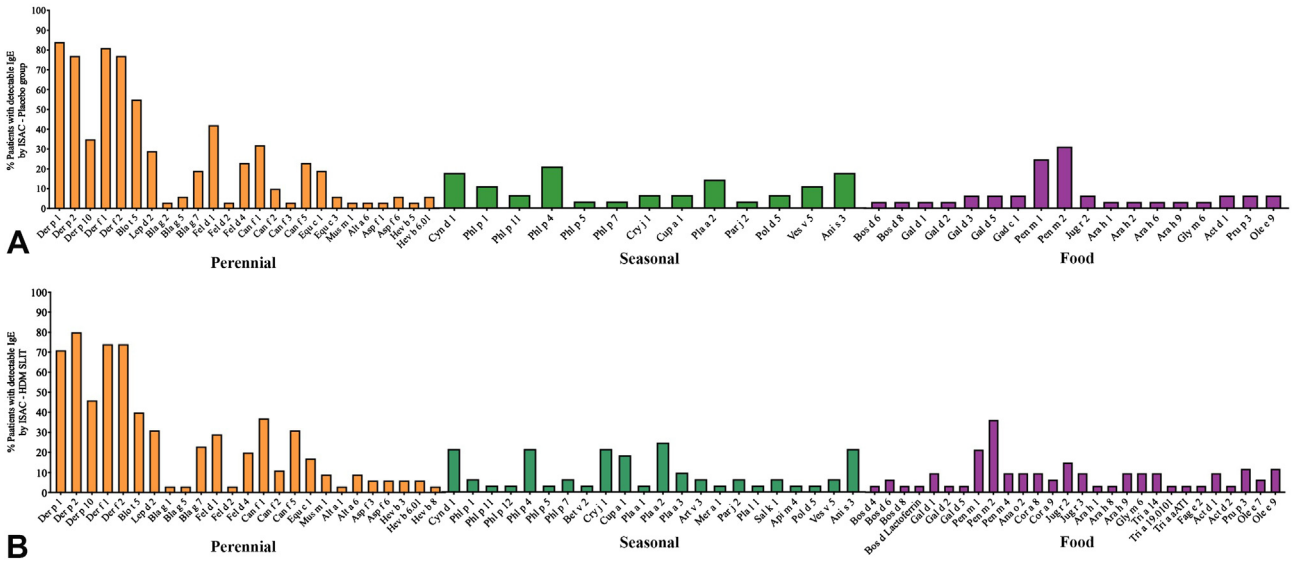

FIGURE 2. Sensitization profile shown as percentage of patients with detectable IgE to allergens on ImmunoCAP-ISAC, in (**A**) the placebo group and (**B**) the HDM SLIT group. The highest frequency of sensitization was observed for mite allergens in both groups. ImmunoCAP-ISAC levels are presented in Tables E1 and E2. *ISAC*, Immunosorbent Allergen Chip.

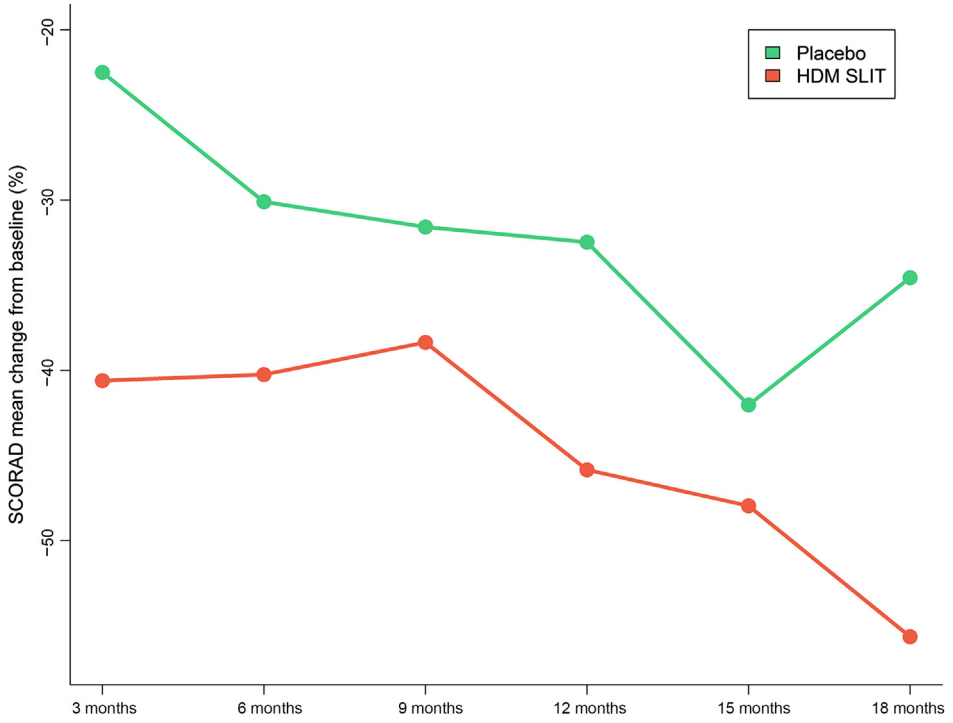

FIGURE 3. Mean decreases in the SCORAD score over time as compared with baseline, in the HDM SLIT and placebo groups. After 18 months of treatment, the SCORAD score decreases from baseline were 55.6% in the HDM SLIT group and 34.5% in the placebo group, with a significant mean difference of 20.4 (95% CrI, 3.89-37.3; in this analysis, statistical significance is defined by a 95% CrI excluding 0).

provided the flexibility to perform an induction phase and entailed progression of treatment according to eventual reactions; this may have contributed to the safety of the treatment. These are important issues in geographic areas where tablets are not available and/or where autoinjectable epinephrine may not be readily accessible in conjunction with SLIT tablets.

The efficacy and safety of SLIT in patients with AD have been investigated in a few randomized, placebo-controlled

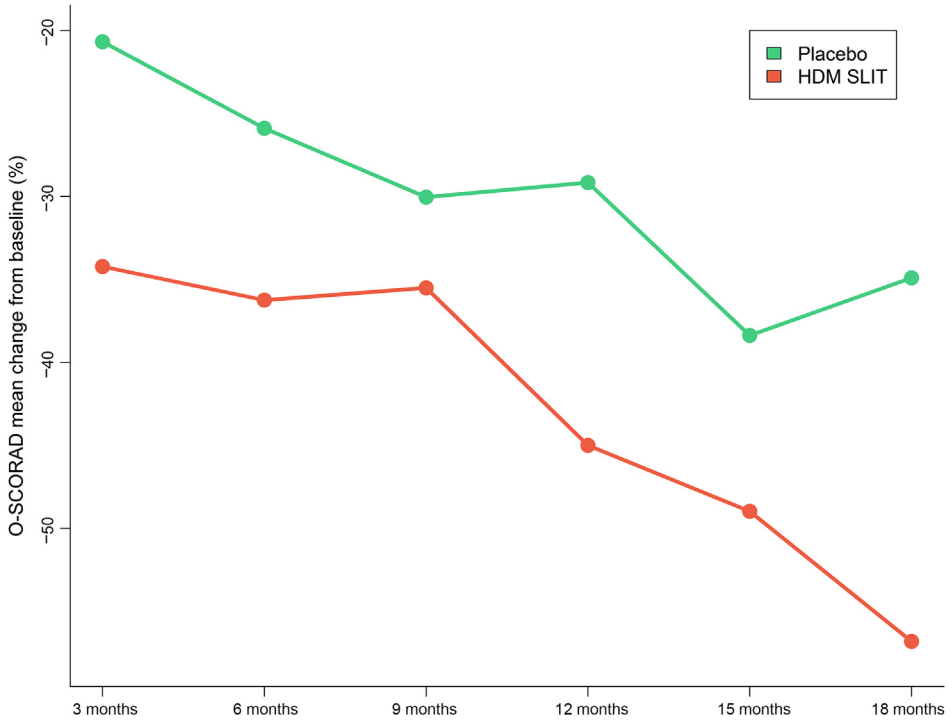

FIGURE 4. Mean decreases in the O-SCORAD score over time as compared with baseline, in the HDM SLIT and placebo groups. After 18 months of treatment, the O-SCORAD score decreases from baseline of 56.8% and 34.9% were present in the HDM SLIT group and the placebo group, respectively, at 18 months, with a significant difference of 21.3 (95% CrI, 0.66-41.81; in this analysis, statistical significance is defined by a 95% CrI excluding 0).

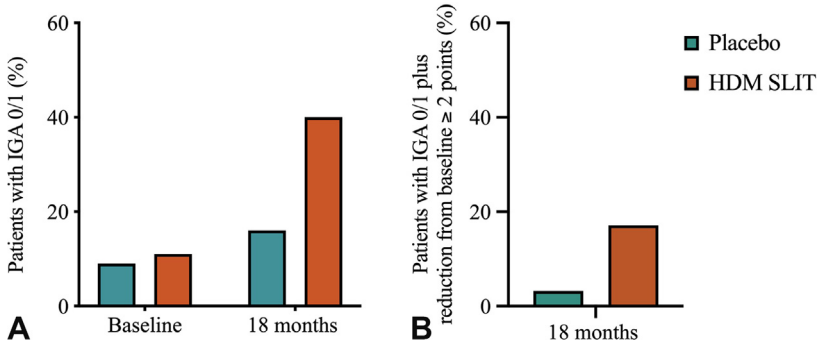

FIGURE 5. Proportion of patients who achieved an IGA response over the 18-months treatment period. (**A**) Significantly more patients in the HDM SLIT group had an IGA 0/1 at 18 months as compared with the those in placebo group (RR, 2.63; 95% CI, 1.09-6.39; in this analysis, statistical significance is defined by a 95% CI excluding 1). (**B**) More patients in the HDM SLIT group had an IGA 0/1 plus a reduction from baseline of 2 or more points at 18 months as compared with those in the placebo group (6 of 35 HDM SLIT and 1 of 31 placebo); however, this difference was not significant (RR, 2.14; 95% CI, 0.34-13.69).

trials.[22,23,41-43] In children aged 5 to 16 years, the administration of HDM SLIT for 18 months resulted in clinical improvement in terms of the severity of AD and decrease in medication use in the group with mild and moderate disease (SCORAD score <40 points) compared with placebo; however, no significant effect was observed in the group with severe AD.[42] A more recent multicenter study performed in China showed that SLIT with *D farinae* extract for a period of 9 months resulted in a decrease in the SCORAD score in adult patients with mild and moderate AD; however, there was a marked placebo effect and lack of significant differences for most outcomes.[43]

Our results raised an important issue, of which measurement instruments would be the most appropriate to objectively assess disease severity in patients with AD. The SCORAD has been extensively validated and is widely used as a clinician-reported outcome instrument.[18,21,42] The adapted version O-SCORAD assesses the 6 objective components of SCORAD (erythema, edema/induration/papulation, excoriation,

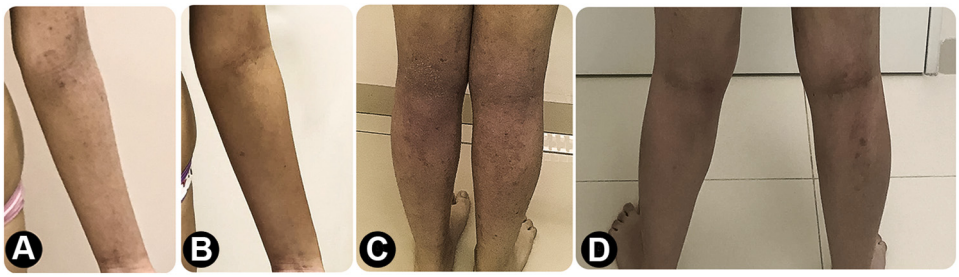

FIGURE 6. (**A** and **C**) A 15-year-old female patient presenting intensely pruritic, erythematous, liquenified, excoriated lesions in the skin of antecubital and popliteal fossae at baseline. (**B** and **D**) After 18 months of HDM SLIT, she showed marked improvement in her AD, with remaining hyperchromic residual lesions and mild pruritus in these areas. SCORAD values were 69 and 29; O-SCORAD values were 55 and 21.5, before and 18 months after HDM SLIT, respectively. Her total IgE at baseline was 5480 IU/mL. Photographs reproduced with permission from the patient and her parents.

TABLE II. Treatment adverse events (MedDRA HLT or PT)

Treatment adverse events	HDM SLIT (n = 35)	Placebo (n = 31)
Headache	15 (42.9)	20 (64.5)
Abdominal pain	8 (22.9)	6 (19.3)
AD aggravated*	1 (2.9)	5 (16.1)
Decreased appetite	1 (2.9)	5 (16.1)
Product use complaint	5 (14.2)	0
Thirst	1 (2.9)	4 (13)
Hyperhidrosis	1 (2.9)	0
Alopecia	1 (2.9)	0
Aphthous ulcer	1 (2.9)	0
Dizziness	1 (2.9)	2 (6.5)
Labyrinthitis	1 (2.9)	0
Abdominal pain upper	1 (2.9)	3 (9.7)
Nausea	2 (5.7)	3 (9.7)
Vomiting	2 (5.7)	1 (3.2)
Tingling tongue	1 (2.9)	2 (6.5)
Dyspnea	2 (5.7)	1 (3.2)
Somnolence	0	2 (6.5)
Constipation	1 (2.9)	1 (3.2)
Cough	1 (2.9)	1 (3.2)
Dyspepsia	0	1 (3.2)
Taste disorder	0	1 (3.2)
Weight decreased	0	1 (3.2)
Wheezing	0	1 (3.2)
Paresthesia	0	1 (3.2)
Lacrimation increased	0	1 (3.2)
Dysuria	0	1 (3.2)
Seizure	0	1 (3.2)
Perioral dermatitis	0	1 (3.2)
Kaposi's varicelliform eruption	0	1 (3.2)
Sleep terror	1 (2.9)	0
Edema mucosal	1 (2.9)	0
Pain of lower extremities	1 (2.9)	0

*AD flare within 48 h following application of SLIT.

lichenification, oozing/crusting, and dryness/xerosis) along with body surface area, but removes the 2 subjective patient-reported outcome scales of SCORAD that assess daily itch and sleeplessness, and adds 10 additional points for disfiguring or functionally limiting lesions.[18,44] However, EASI has been preferred over O-SCORAD because the grading of disease severity is performed on the basis of its average degree in each region rather than the selection of the most representative lesion, and it allocates greater weight to the disease extent. Of note, EASI does not account for oozing/crusting and dryness, which may be important components of disease severity. Recently, a core outcome set to be used in AD clinical trials has been recommended by the Harmonizing Outcome Measures for Eczema initiative, which includes EASI and Patient Oriented Eczema Measure as the preferred instruments for clinician-reported signs and patients-reported symptoms, respectively; DLQI, Children's DLQI, and Infant's Dermatitis Quality of Life Index as core outcome instruments for assessing health-related quality of life; Recap of Atopic Eczema and Atopic Dermatitis Control Tool for long-term control; and Peak Pruritus Numerical Rating Scale-11 past 24 hours for measuring itch intensity in trials including older children and adults.[45] Interestingly, the Harmonizing Outcome Measures for Eczema initiative endorses using the Patient Oriented Eczema Measure, the Patient-oriented PO-SCORAD index, or both for measuring atopic eczema symptoms in clinical practice.[45] Even though our results did not show significant differences in EASI scores, significant decreases in the values of SCORAD tools after 18 months of HDM SLIT as compared with placebo may indicate the clinical efficacy of this added treatment. In addition, a significant decrease in IGA 0/1 may support the results of SCORAD tools.[18]

Another relevant aspect is the minimal important change (MIC) in SCORAD and other tools used to evaluate the severity of AD. In the present study, an absolute 15-point drop was chosen on the basis of our clinical experience of using primarily SCORAD in the follow-up of our patients with moderate and severe AD. After our study was conducted, Silverberg et al[46] demonstrated that the absolute MIC varied across the different levels of AD severity at baseline, and MIC thresholds were defined as 2.7 to 15.8 for mild AD, 17.5 to 23.3 for moderate AD, and 22.3 to 29.2 for severe AD at baseline.[46] Previous lower thresholds for absolute SCORAD and O-SCORAD MIC values of 8.7 and 8.2, respectively, were identified among children and/or adult patients with moderate to severe AD in randomized clinical trials.[47] Our MIC estimate of a 15-point decrease in

SCORAD was within the values previously associated with significant clinical improvement.

A major strength of our study is the fact that the same investigator (S.S.L.) evaluated all patients throughout the study, allowing for more personalized care, reinforcement of topical therapy, and prompt recognition of complications, particularly infection requiring systemic antibiotics, and psychological issues. This feature may have minimized investigator-dependent bias, improving the consistency of clinical score assessments throughout the study period. As with many IT trials, the placebo effect in the present study was very large, reinforcing the need to conduct double-blind placebo-controlled trials to investigate the clinical efficacy of IT.[42,43]

Our study had several limitations. Treatment duration may not have been optimal, and further efficacy could be documented beyond 18 months of therapy.[48] Our weekly maintenance dose of major allergens Der p 1 plus Der p 2 of approximately 0.9 μg was lower than that in previous studies; however, few studies have provided levels of Der p 1 and Der p 2 in Dpt extracts used for SLIT.[48] It is possible that the dose-finding results in respiratory allergies may not be applicable to AD. More than 80% and 40% of our patients presented with allergic rhinitis and asthma, respectively; however, evaluation of the effectiveness of HDM SLIT in concomitant respiratory allergy was beyond the scope of the present study. Although higher doses of HDM SLIT could potentially provide additional benefit, the dose chosen in the present study was consistent with an affordable cost for a maintenance SLIT regimen for Brazilian patients and their families, and with treatment adherence, because it was administered 3 times a week, as previously reported.[42] The baseline differences in severity, patient age, and treatments could pose a problem in analyzing the true effects of HDM SLIT; however, the small sample sizes for subgroup analysis prompted us to evaluate the group as a whole. To minimize this limitation, stratified randomization was performed to allow for a balanced distribution of patients according to age (<12 and ≥ 12 years) between the HDM SLIT and placebo groups. Although AD may be clinically heterogeneous and share common as well as specific immunologic mechanisms among children and adults,[17] a remarkable feature of the disease is the efficacy of the treatment with dupilumab, which targets type 2 responses, in both children and adults with moderate and severe disease.[6-9] Therefore, pooling children and adults with AD in the present study would be adequate. The benefits of IT have been established in patients with IgE-mediated diseases, and the mechanisms involve an increase in the number and activity of regulatory T cells, which also downregulate type 2 responses. Moreover, many of our patients showed IgE sensitization to other inhalants in addition to HDM allergens, including those derived from cats and dogs, and to a lesser extent from pollens and molds, which were not included in the SLIT preparation due to the blinded nature of the study. It is unclear whether using a mixture of allergens would improve the efficacy of SLIT.[38,49] The dropout rate (27%) in the present study was high; however, it was consistent with that reported in previous studies on allergen-specific IT for patients with AD.[21,23,42,43] Finally, despite the clinical improvement, we did not observe any significant benefit in quality of life among patients who received HDM SLIT as compared with placebo; however, DLQI is not a specific tool for AD, and part of the study was conducted during the coronavirus disease 2019 pandemic, which may have influenced the quality of life in this scenario.

CONCLUSIONS

We have shown that HDM SLIT for 18 months resulted in clinical improvement of HDM-sensitized patients with AD, as judged by SCORAD tools for measuring the severity of AD. Our results warrant further studies to investigate the optimal duration and dose as well as the long-term efficacy and possibility of sustained effects of HDM SLIT in patients with AD.

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ONLINE REPOSITORY

OTHER SECONDARY OUTCOME MEASURES

Patients were evaluated using EASI, DLQI, VAS of symptoms, and pruritus scores at 3, 6, 9, 12, 15, and 18 months of treatment (Figures E1, E2, and E3).

ADDITIONAL ADVERSE EVENTS

One patient, a 12-year-old girl, reported urticaria, cough, and shortness of breath approximately 8 hours after receiving 1 drop of the 1:100 v:v dilution, leading to an emergency department visit. Subsequently, we performed an in-hospital challenge using the same dose. After 3 hours, she presented with mild urticaria in the face and trunk that resolved with oral antihistamine; after 10 hours, she presented with mild urticaria and periorbital edema, nasal and ocular itching, headache, and watery eyes, and was treated with oral antihistamine and prednisone with complete resolution after an overnight stay in hospital. There was no drop in blood pressure or peak flow, and no dyspnea or wheezing on auscultation, and no epinephrine was required. We chose to withdraw her from the study. At the end of the study, we found out that she had been assigned to the placebo group. She is now receiving treatment with dupilumab, with significant improvement in her AD. Trigger factors for the reactions were unclear; her mother reported the use of dipyrone (metamizole) before the first reaction, but no suspected trigger was identified for the second reaction.

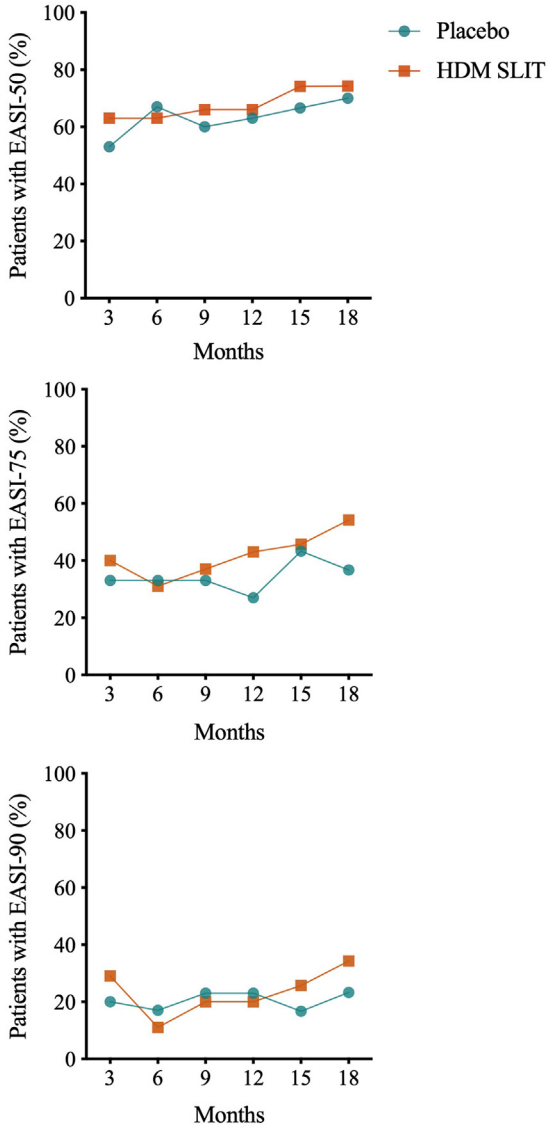

FIGURE E1. The proportion of patients who achieved an (**A**) EASI-50, (**B**) EASI-75, and (**C**) EASI-90 response over the 18-month treatment period. No significant differences were observed for HDM SLIT and placebo groups. *EASI*, Eczema Area and Severity Index; *EASI-50*, improvement of at least 50% in EASI score from baseline; *EASI-75*, improvement of at least 75% in EASI score from baseline; *EASI-90*, improvement of at least 90% in EASI score from baseline.

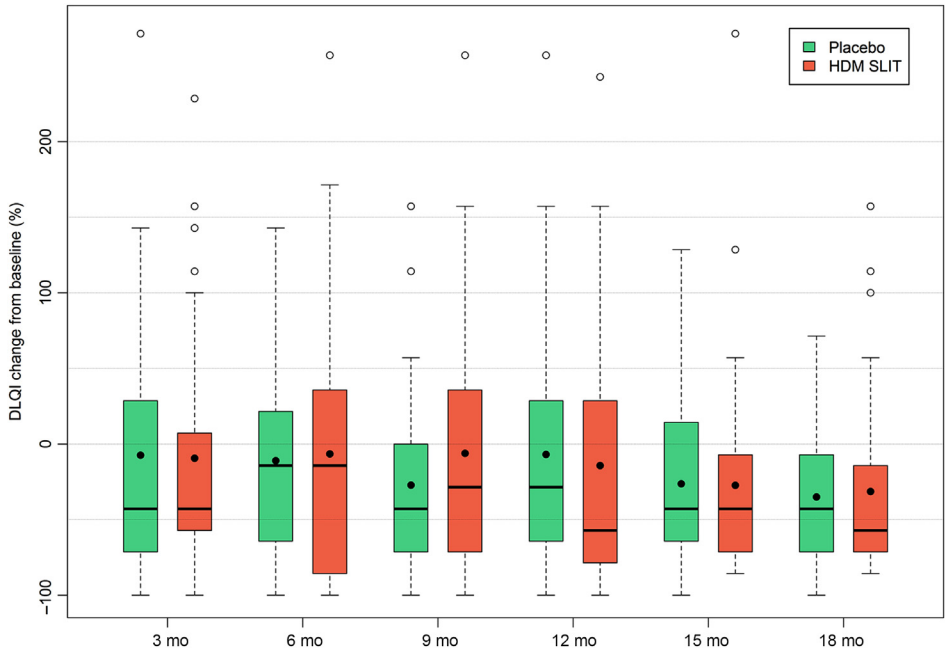

FIGURE E2. Decreases in DLQI over time as compared with baseline in the HDM SLIT and placebo groups. No significant differences were observed for DLQI in patients receiving HDM SLIT compared with those receiving placebo.

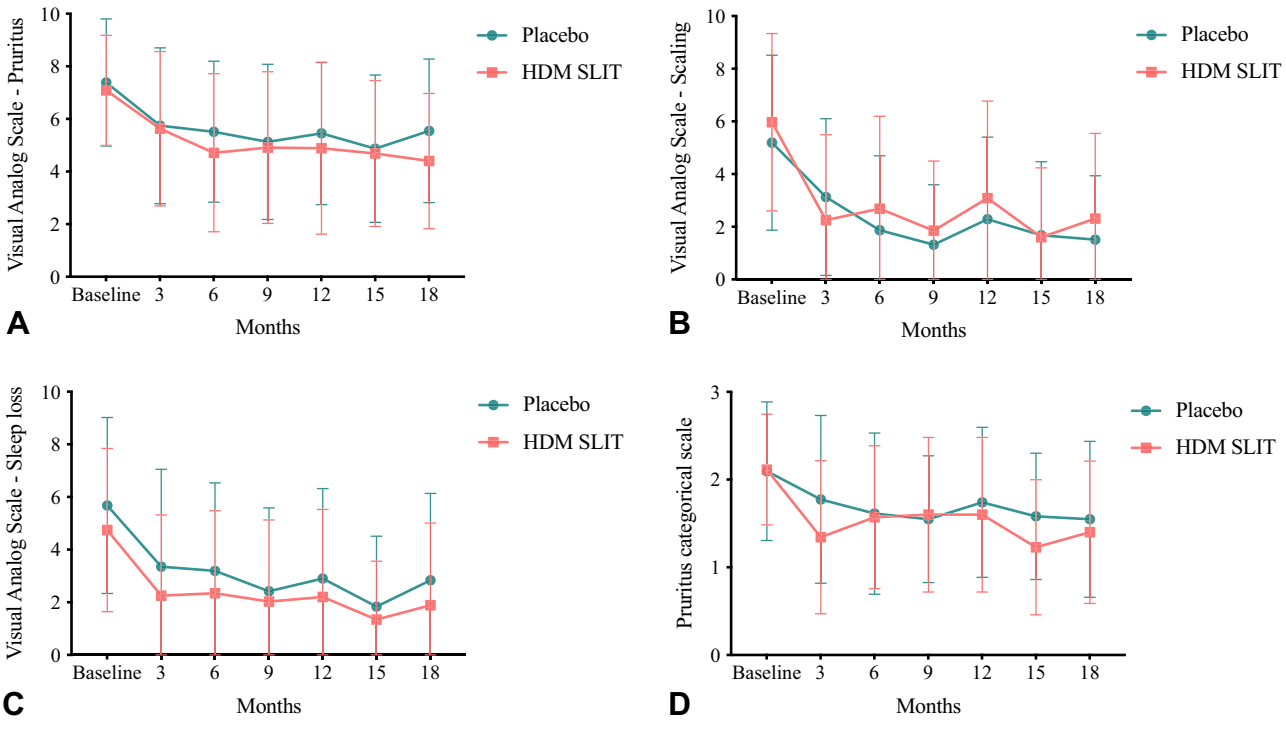

FIGURE E3. (**A**) VAS of symptoms of pruritus (0-10); (**B**) scaling (0-10); and (**C**) sleep loss (0-10); (**D**) pruritus categorical scale (0, none; 1, mild; 2, moderate; 3, severe pruritus) in the HDM SLIT and placebo groups. No significant differences were observed for VAS of symptoms or pruritus scale in patients receiving HDM SLIT and placebo. Mean values and SD (bars) are shown.

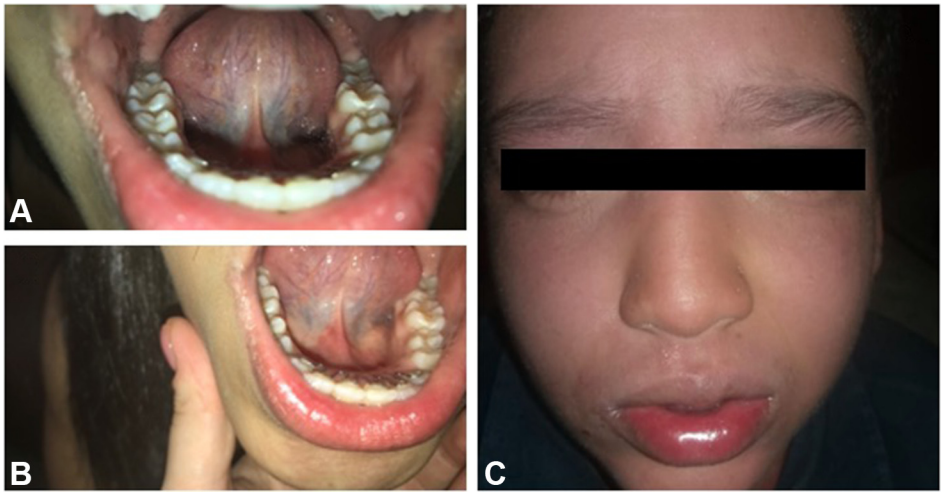

FIGURE E4. Adverse events during HDM SLIT treatment. (**A**) Normal oral mucosa before application of HDM SLIT in the office. (**B**) Local edema and enanthema of sublingual mucosa 5 minutes after application of 8 drops of 1:10 v:v HDM SLIT in a 17-year-old study participant; pretreatment with antihistamine subsequently prevented the reaction. (**C**) Lip and periorbital swelling, accompanied by cough and mild dyspnea, in a 13-year-old boy, 3 hours following administration of HDM SLIT maintenance dose; patient had received oral antihistamine 1 hour after the SLIT dose, and symptoms resolved within the next few hours without need for other medications; however, he was excluded from the study. Photographs reproduced with permission from the patients and/or their caregivers.

TABLE E1. Sensitization profile determined by ISAC of patients with AD who received placebo or HDM SLIT for 18 mo

Source	Allergen	No. of patients with detectable IgE—placebo group (n = 31)	Mean, ISU (range)	No. of patients with detectable IgE—HDM SLIT (n = 35)	Mean, ISU (range)
Perennial					
Mites	Der p 1	26	42.2 (0.37-101.7)	25	52.9 (4.67-106.1)
	Der p 2	24	61.7 (0.73-147.7)	28	56.2 (0.55-131.53)
	Der p 10	11	38.8 (0.4-138.4)	16	37.2 (0.44-142.88)
	Der f 1	25	47.6 (1.97-127.5)	26	40.8 (0.43-120.94)
	Der f 2	24	49.6 (0.42-129.01)	26	44.7 (7.66-110.67)
	Blo t 5	17	0.3 (0.38-52.89)	14	15.8 (0.48-76.44)
	Lep d 2	9	27.2 (0.73-85.45)	11	6.9 (0.4-26.55)
Cockroach	Bla g 1	0	NA	1	19.89
	Bla g 2	1	0.4	0	NA
	Bla g 5	2	0.5 (0.49-0.57)	1	2.62
	Bla g 7	6	63.5 (12.1-120.3)	8	61.4 (7.04-140.16)
Cat	Fel d 1	13	11.5 (0.47-83.59)	10	14.2 (1.01-39.79)
	Fel d 2	1	7.49	1	0.4
	Fel d 4	7	2.2 (0.36-5.38)	7	3.1 (0.7-3.75)
Dog	Can f 1	10	14.5 (0.44-62.57)	13	21.6 (0.49-135.71)
	Can f 2	3	11.5 (10.39-13.51)	4	28.9 (8.99-80.14)
	Can f 3	1	8.16	0	NA
	Can f 5	7	37.6 (1.99-104.69)	11	23.5 (0.48-94.11)
Horse	Equ c 1	6	2.2 (1.51-4.46)	6	6.2 (0.76-19.25)
	Equ c 3	2	1.4 (1.05-1.73)	0	NA
Mouse	Mus m 1	1	0.37	3	0.6 (0.4-0.67)
Fungi	Alt a 1	0	NA	1	91.06
	Alt a 6	1	0.35	2	1.7 (1.54-1.79)
	Asp f 1	1	0.43	0	NA
	Asp f 3	0	NA	3	2.5 (2.34-2.54)
	Asp f 6	2	24.2 (0.93-47.41)	1	13.48
	Cla h 8	0	NA	1	0.55
Latex	Hev b 1	0	NA	0	NA
	Hev b 3	0	NA	0	NA
	Hev b 5	1	23.3	0	NA
	Hev b 6.01	2	1.1 (0.83-1.41)	3	13.4 (0.35-39.15)
	Hev b 8	0		2	15.3 (0.35-30.17)
Seasonal					
Grasses	Cyn d 1	5	2.9 (0.4-5.34)	7	13.1 (0.55-69.88)
	Phl p 1	3	5.8 (0.37-11.62)	2	25.2 (2.43-48.05)
	Phl p 11	2	2.7 (2.11-3.24)	1	15.07
	Phl p 12	0	NA	1	2.18
	Phl p 2	0	NA	0	NA
	Phl p 4	6	1.8 (0.4-7.45)	7	6.9 (0.62-23.23)
	Phl p 5	1	2.37	1	0.5
	Phl p 6	0	NA	0	NA
	Phl p 7	1	27.76	2	1.3 (0.81-1.7)
Trees	Aln g 1	0	NA	0	NA
	Bet v 1	0	NA	0	NA
	Bet v 2	0	NA	1	16.18
	Bet v 4	0	NA	0	NA
	Cor a 1.0101	0	NA	0	NA
	Cry j 1	2	3.3 (1.13-5.39)	7	3.8 (0.35-14.46)
	Cup a 1	2	4 (0.96-7.05)	6	5.8 (0.86-15.92)
	Ole e 1	0	NA	0	NA
	Pla a 1	0	NA	1	1.47
	Pla a 2	4	2.9 (0.52-9.35)	8	4.1 (0.78-12.51)
	Pla a 3	0	NA	3	4 (2.19-5.05)

(continued)

TABLE E1. *(Continued)*

Source	Allergen	No. of patients with detectable IgE—placebo group (n = 31)	Mean, ISU (range)	No. of patients with detectable IgE—HDM SLIT (n = 35)	Mean, ISU (range)
Weeds	Amb a 1	0	NA	0	NA
	Art v 1	0	NA	0	NA
	Art v 3	0	NA	2	0.9 (0.65-1.3)
	Che a 1	0	NA	0	NA
	Mer a 1	0	NA	1	17.44
	Par j 2	1	2.11	2	1.3 (1.01-1.57)
	Pla l 1	0	NA	1	0.97
	Sal k 1	0	NA	2	0.9 (0.73-1.08)
Insects	Api m 1	0	NA	0	NA
	Api m 4	0	NA	1	0.53
	Pol d 5	2	0.7 (0.65-0.8)	1	0.38
	Ves v 5	3	1.2 (0.65-2.44)	2	0.5 (0.35-0.57)
Parasite	Ani s 1	0	NA	0	NA
	Ani s 3	5	52.6 (11.94-132.81)	5	49.5 (6.16-149.04)
Food					
Milk	Bos d 4	0	NA	1	2.15
	Bos d 5	0	NA	0	NA
	Bos d 6	1	2.11	2	0.9 (0.49-1.37)
	Bos d 8	1	0.64	1	2.16
	Bos d Lactoferrin	0	NA	1	0.49
Egg	Gal d 1	1	11.46	3	2.1 (0.97-3.61)
	Gal d 2	1	0.8	1	0.79
	Gal d 3	2	0.6 (0.43-0.79)	0	NA
	Gal d 5	2	0.41 (0.38-0.44)	1	1.97
Fish	Gad c 1	2	10.5 (7.06-14.05)	0	NA
Shrimp	Pen m 1	7	64.4 (0.6-144.09)	7	68.5 (6.86-151.34)
	Pen m 2	9	16.3 (0.5-51.42)	12	12.3 (2.2-49.42)
	Pen m 4	0	NA	3	0.4 (0.42-0.49)
Nuts/walnut	Ana o 2	0	NA	3	1.8 (0.86-3.02)
	Ber e 1	0	NA	0	NA
	Cor a 1.0101	0	NA	0	NA
	Cor a 8	0	NA	3	1.3 (0.35-2.39)
	Cor a 9	0	NA	2	0.9 (0.45-1.39)
	Jug r 1	0	NA	0	NA
	Jug r 2	2	0.6 (0.43-0.78)	5	3.2 (0.62-9.23)
	Jug r 3	0	NA	3	2.7 (2.24-3.61)
Legumes	Ara h 1	1	1.03	1	1.43
	Ara h 2	1	15.79	0	NA
	Ara h 3	0	NA	0	NA
	Ara h 6	1	1.04	0	NA
	Ara h 8	0	NA	1	10.61
	Ara h 9	1	0.54	3	4.4 (0.98-10.8)
	Gly m 4	0	NA	0	NA
	Gly m 5	0	NA	0	NA
	Gly m 6	1	1.6	3	0.4 (0.42-0.51)
Wheat	Tri a 14	0	NA	3	2.4 (0.35-4.12)
	Tri a 19.0101	0	NA	1	2.14
	Tri a aATI	0	NA	1	0.38

(continued)

TABLE E1. *(Continued)*

Source	Allergen	No. of patients with detectable IgE—placebo group (n = 31)	Mean, ISU (range)	No. of patients with detectable IgE—HDM SLIT (n = 35)	Mean, ISU (range)
Buckwheat	Fag e 2	0	NA	1	0.57
Fruits	Act d 1	2	0.9 (0.84-1.03)	3	0.7 (0.36-1.05)
	Act d 2	0	NA	1	3.82
	Act d 5	0	NA	0	NA
	Act d 8	0	NA	0	NA
	Mal d 1	0	NA	0	NA
	Pru p 1	0	NA	0	NA
	Pru p 3	2	0.6 (0.52-0.66)	4	3.5 (1.81-7.54)
Vegetables	Api g 1	0	NA	0	NA
Seed	Ses i 1	0	NA	0	NA
	Ole e 7	0	NA	1	0.53
	Ole e 9	2	1.7 (0.38-3.03)	4	4 (0.47-6.41)

ISAC, Immunosorbent Allergen Chip; *ISU*, ISAC standardized units; *NA*, not applicable.