Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study

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Background: Atopic dermatitis often has an allergic component, and immunotherapy may therefore prove beneficial.

Objective: To assess the effect of sublingual immunotherapy (SLIT) in children with atopic dermatitis.

Methods: Children age 5 to 16 years with atopic dermatitis (Scoring Atopic Dermatitis [SCORAD] > 7) and sensitization to dust mites alone, without food allergy or chronic asthma, were enrolled in a randomized, double-blind, placebo-controlled study and stratified according to disease severity. SLIT or placebo was given for 18 months in addition to standard therapy. SCORAD, visual analog scale, and rescue medication consumption were recorded at 3-month intervals.

Results: Fifty-six children were enrolled, and 28 were allocated to SLIT. Forty-eight completed the study, with 2 dropouts in the active and 6 in the placebo group. The difference from baseline in the SCORAD was significant ($P = .025$) between the 2 groups starting from month 9. Similarly, there was a significant reduction in the use of medications only in the active group. A trend toward significance was seen for the visual analog score only in the active group versus baseline ($P = .07$). A significant difference in the considered parameters was found only in patients with a mild-moderate disease, whereas severe patients had only a marginal benefit. SLIT had to be discontinued in 2 patients because of exacerbation of dermatitis.

Conclusion: Sublingual immunotherapy to dust mite improves mild-moderate atopic dermatitis.

Clinical implications: Sublingual immunotherapy may represent an additional therapeutic tool for the treatment of extrinsic atopic dermatitis in properly selected children. (J Allergy Clin Immunol 2007;120:164-70.)

Key words: Atopic dermatitis, house dust mites, sublingual immunotherapy

Abbreviations used
AD: Atopic dermatitis
DBPCFC: Double-blind, placebo-controlled food challenge
HDM: House dust mite
SCORAD: Scoring Atopic Dermatitis
SIT: Specific immunotherapy
SLIT: Sublingual immunotherapy
VAS: Visual analog scale

Atopic dermatitis (AD),[1] despite the relatively high prevalence, still remains partly obscure in its pathogenic mechanisms. Although it cannot be considered a typical allergic disease, there is convincing evidence that in some patients, aeroallergens, especially house dust mite (HDM) or food allergens, play a relevant role in eliciting or aggravating the eczematous skin lesions and may contribute to the flare-ups of eczema in those patients.[2-5] On the basis of these observations, 2 types of AD have been identified. The allergic or extrinsic form affects about 80% of the patients with AD and occurs in the context of an IgE sensitization toward foods or environmental allergens. Intrinsic AD is independent of atopy and allergy, it is associated with normal IgE levels, and no allergen sensitization is detectable.[6] Because of the complexity of the diseases, several different therapeutic approaches are currently in use, but a truly curative therapy does still not exist.[7,8]

It is well known that specific immunotherapy (SIT), in association with drug therapy, is highly effective in IgE-mediated allergic diseases such as aeroallergens and *Hymenoptera* venom hypersensitivity.[9] SIT modifies at the earliest steps the immune response to allergens[10]; thus, it can be hypothesized that, at least in the extrinsic form of AD, it could be of some clinical benefit. This hypothesis is intriguing; in fact, some clinical trials investigating the effects of SIT in AD have been performed, some of them reporting positive results (see review[11]). Nevertheless, most studies were observational, open, or conducted in adults. For about 20 years, the sublingual route for SIT administration (sublingual immunotherapy [SLIT]) has been commercially available and routinely used in Europe.[12] In addition to the proven clinical efficacy,[13,14] SLIT has a satisfactory safety profile, and it is well tolerated in small children.[15] SLIT can be considered

as a viable alternative to injection SIT in the pediatric age; therefore, it represents an attractive opportunity to investigate the clinical effect of SIT in AD. We report herein the results of a randomized, double-blind, placebo-controlled study with SLIT in children with symptomatic AD and concomitant sensitization to HDM.

METHODS

Study plan

The study was designed as randomized, double-blind, and placebo-controlled, with 2 parallel groups. Children age 5 years or older with actual AD, but without evidence of persistent bronchial asthma or food allergy, were enrolled for this study. After a baseline observation of 1 month, they were stratified according to the severity of AD (Scoring Atopic Dermatitis [SCORAD] 8-40, mild-moderate; SCORAD > 40, severe) and randomized to receive, in addition to rescue therapy, either SLIT or placebo for 18 months. During the trial, the SCORAD and a visual analog scale (VAS) score were assessed at several time points. Adverse events were carefully recorded throughout the whole study, as well the overall consumption of medications. The study was approved by the local Ethics Committee, and all the parents signed a written informed consent.

Patients

Children of both sexes, age between 5 and 16 years, were enrolled. Inclusion criteria were the following:

1. Clinical history of chronic AD without evidence of spontaneous improvement at age 5 years.
2. IgE-mediated sensitization to HDM, assessed by positive skin prick test (wheal > 3 mm) and positive CAP-RAST assay (class III or greater). Pollen sensitizations were admitted, provided that no relevant exacerbation of AD during the pollen seasons was reported.
3. If a positive or suggestive history of food allergy in the previous years with positive skin tests was reported, those foods had to be fully tolerated at the enrollment, as confirmed by a double-blind, placebo-controlled food challenge.
4. A SCORAD of 8 or greater.[16]
5. FEV$_1$ greater than 80% of predicted value.

Exclusion criteria were the following:

1. Bronchial asthma requiring regular treatment with inhaled steroids.
2. Actual persistent food allergy.
3. Any previous course of immunotherapy.
4. Severe systemic disorders (eg, cystic fibrosis, diabetes, celiac disease) or malignancies.

The children were stratified according to the severity of their AD (mild-moderate or severe) and randomized to active or placebo treatment according to computer-generated code.

Diagnostic procedures

Skin prick tests were performed according to recommendations by using a panel of biologically standardized allergens (ALK-Abelló, Milan, Italy) that included mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grasses, olive, birch, cat and dog dander, mugwort, *Parietaria*, *Alternaria*, *Cladosporium*, egg, milk proteins, hazelnut, peanut, wheat, fish, peach, apple, and tomato. In the case of allergic sensitization to foods, a DBPCFC was performed to confirm that the sensitization was not clinically relevant. DBPCFCs were performed according to the standardized protocols.[17,18]

Pulmonary function test was performed with a Multispiro-PC spirometer (Burke and Burke, Wuzburg, Germany). The best of 3 maneuvers, starting from vital capacity, was selected. In subjects with a clinical history suggestive of asthma, a methacholine challenge (according to Chai et al[19]) was performed.

SLIT and concomitant treatments

The prescribed SLIT (Anallergo, Florence, Italy) was prepared as a glycerinated solution for sublingual drops. The drops had to be taken in the morning before breakfast, kept under the tongue for about 2 minutes, and then swallowed. The extract was standardized through a combined RAST inhibition and bioequivalence method, and the potency was expressed as RAST units per milliliter. The build-up phase of about 15 days involved the administration of the extract at 3 progressively increasing concentrations of 100, 1000, and 10,000 RAST units per milliliter. In the higher concentration vial, the content of allergen was 4.3 μg/mL Der p 1 and 3.5 μg/mL Der f 1. The drops (50 μL each) had to be taken starting with 1 drop from the first vial, increasing by 1 drop every day up to 5 drops, and then repeating the steps with the next vial. The maintenance dose was of 5 drops from vial 3, and had to be assumed 3 times a week for 18 months. The updosing was performed in hospital under medical supervision. The placebo was indistinguishable from the active one in appearance, color, and taste.

Children and parents were carefully instructed on the correct use of the treatment, and additional written instructions were given. A physician was available for phone contact and extra visits at the clinic during the whole study. Allowed medications for AD in all patients were short courses (3 days) of topical fluticasone propionate and/or oral hydroxyzine on demand in the case of worsening pruritus, itching, edema, or oozing. In the case of cutaneous superinfection, the physician could prescribe a 6-day course of clarithromycin (15 mg/kg/d). No other treatment, including moisturizers, was allowed during the study.

Evaluation parameters

All the patients were followed up with regular clinic visits during the whole study. The change in SCORAD versus baseline was the primary outcome. The baseline SCORAD was assessed before randomization (run-in period of 1 month) and then after 3, 6, 9, 12, 15, and 18 months of treatment. A Δ SCORAD (difference from baseline) was calculated for analysis. At the same time points, parents were asked to quantify the overall AD symptoms on a VAS ranging from 0 (no symptoms at all) to 10 (very severe symptoms). To fill the VAS, they had to answer the question, "How was the eczema in this last month?" The use of rescue medications was recorded throughout the study, and the total amount in the 18 months was calculated. The use of medications was scored 1 point for each dose of oral hydroxizine or topical steroid (fluticasone ointment) and 2 points for each dose of oral clarithromycin in the 6-day course. The latter was given only in the case of superinfection.

Parents were instructed to record on an appropriate card any local or systemic reaction after each SLIT administration. The following symptoms were evaluated on a 0 to 3 scale (0, no symptoms; 3, severe symptoms): rhinitis; conjunctivitis; itching/swelling in the mouth, lips, throat, or face; generalized itching; urticaria; cough; and wheezing. At each scheduled visit, the use of medications and the severity of symptoms were checked as well as side effects.

Statistical analysis

The sample size was calculated to detect a reduction of 20% or more in SCORAD with a 5% significance level and a power of 95%. Because the effects of SIT, especially for HDM, become detectable over months, the efficacy analyses were performed on a per protocol basis, whereas the safety was assessed on the intention-to-treat population. The between-groups difference was analyzed by the

TABLE I. Demography and clinical characteristics of the enrolled children at baseline

	SLIT	Placebo
N	28	28
Sex (male/female)	15/13	12/16
Mean age (y)	10	11
Age range (y)	5-16	5-16
Duration of AD, mean ± SD (y)	6.7 ± 2.3	6.9 ± 2.5
Mild-moderate AD with SCORAD > 40	14	14
SCORAD in mild-moderate patients	32 ± 7	29 ± 5
Total IgE, mean ± SD (kU/L)	560 ± 85	486 ± 51
Rhinitis, n (%)	3 (10.7)	4 (14.2)
Rhinitis + intermittent asthma, n (%)	4 (14.2)	2 (7.1)
Only intermittent asthma, n (%)	7 (25.0)	6 (21.4)
HDM specific IgE, means ± SDs (kU/L)	10.6 ± 2.8	9.2 ± 1.6
Sensitization to foods, n (%)	9 (32.1)	11 (39.3)
Milk	5	6
Egg	3	3
Milk + egg	1	2
Other + ties to aeroallergens, n (%)	5 (18)	2 (7)

Mann-Whitney *U* test, whereas the Wilcoxon test was used for intra-group comparisons. All tests were 2-tailed, and *P* values less than .05 were considered significant.

RESULTS

Patients

Fifty-six children, age between 5 and 16 years (mean age, 10.5 years; 27 boys) were enrolled in the study and randomized so that 28 were allocated to the active SLIT and the remaining to placebo. All patients had skin and serum sensitization to dust mite. Twenty patients, 9 active and 11 placebo, had positive history for food allergy, with positive skin tests, but none proved positive at the DBPCFC with the sensitizing foods (11 milk, 6 egg, 3 both). The 2 groups were well matched for demography and clinical characteristics, as shown in Table I. Forty-eight patients (85% of the enrolled) completed the study. Eight children (2 SLIT and 6 placebo) dropped out during the first 6 months. The children from the placebo group withdrew for the following reasons: 1 moved out of area, 3 were noncompliant with the protocol, and 2 were lost to follow-up. Two children from the active group withdrew because of worsening of AD symptoms, with generalized itching and/or flares after vaccine administration. Five patients of the active group and 2 of the placebo group displayed a concomitant sensitization to pollens, but none of them had a clinical history of seasonal exacerbation of AD or a positive methacholine test (provocative dose > 2 mg/mL) during the pollen seasons. All the children who had a skin positivity to foods (milk and/or egg) proved negative to the DBPCFCs.

The dose administered on maintenance was about 3.3 μg Der p 1 and 2.7 μg Der f 1 per week, around 9 times greater than the subcutaneous dose. All the patients who terminated the study completed the assessments. The planned maintenance dose, 5 drops from the top vial, was reached without any problem by all patients but 2 of the active group.

Clinical efficacy

As shown in Fig 1, a significant improvement versus baseline was seen only in the active group starting from month 9, when the Δ SCORAD became significantly different between the 2 groups (*P* = .0025). No significant difference could be detected in the VAS scores between groups and versus baseline at any time point, although an overall increase versus baseline (+13.1%) in the placebo group and a decrease in the active group (–10.3%; *P* = .07) was observed at the end of the study (Fig 2) Also, a significant difference between the 2 groups in the use of rescue drugs was seen. The total drug score in the 18 months of the study was 171 ± 45 in the SLIT group and 346 ± 68 in the placebo (Wilcoxon *P* = .03). The number of days with at least 1 rescue medication used was 158 ± 41 in the placebo group and 93 ± 24 in the SLIT group (*P* = .01).

We performed a separate analysis for the subgroups of patients with mild-moderate (SCORAD < 40) and severe AD (SCORAD > 40). In the children with mild-moderate AD, the Δ SCORAD significantly improved starting from month 9 in the active group versus placebo (Mann-Whitney *P* < .0005; Fig 3, *A*), whereas no change was observed in the patients with severe AD (Fig 3, *B*). Similarly, the VAS showed in the actively treated mild-moderate patients a decrease starting from month 9 versus baseline (Wilcoxon *P* = .002) and versus placebo (Mann-Whitney *P* = .001; Fig 4, *A*), whereas no change versus baseline was observed in the placebo group. At the end of the study, the overall reduction in the VAS in the active group was –39.2%. No change at all was detectable in patients with severe AD (Fig 4, *B*). The medication intake score in the 2 subgroups of patients is summarized in Fig 5. A significant difference between SLIT and placebo recipients could be found only in the mild-moderate patients (*P* = .01).

Adverse events

Tiredness was reported by 6 patients in the active group and 1 patient in the placebo group. One patient in the active group reported headache. Four local delayed reactions (> 1 hour) were reported in 4 active patients during the build-up with the first dose from the first vial: 1 had swelling of the mouth, lips, and face, and 3 had oral itching. All these side effects were mild, resolved spontaneously, and did not require treatments or dose adjustments. The 2 active SLIT patients who dropped out displayed intense generalized itching and flares about 1 hour after the administration of the vaccine and had to be treated with intramuscular chlorpheniramine and betamethasone. They were excluded from the study after the third attempt.
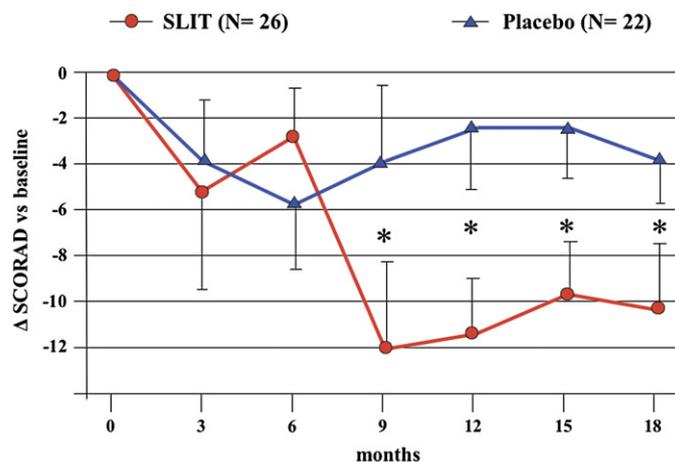
FIG 1. Change from baseline (Δ SCORAD) in the SLIT and placebo groups at the different time points. *Significant differences between groups.
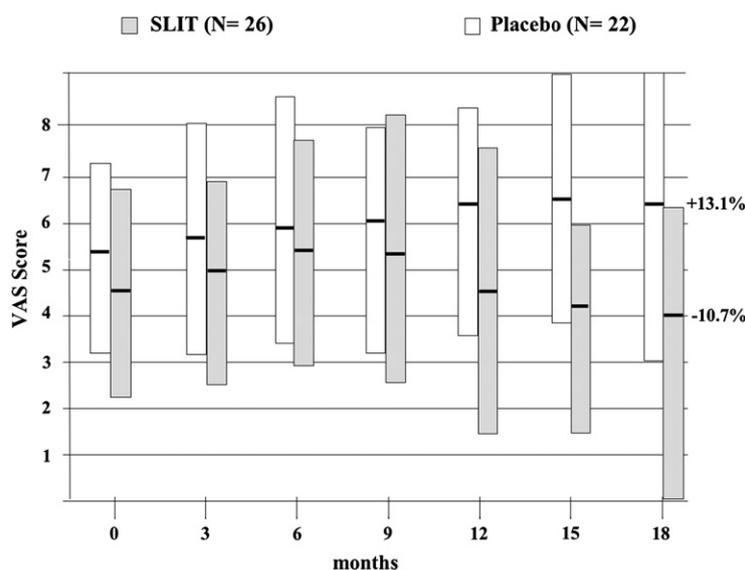

FIG 2. VAS scores (median, range) in the SLIT and placebo groups at the different time points. The *box* represents the range. The median is marked as a *thick line*.

DISCUSSION

Currently, no specific curative treatment is available for children with AD.[7,8] Of course, hydration of the skin and maintenance of an intact skin barrier are the cornerstone of an adequate management, and topical corticosteroids still remain the primary anti-inflammatory therapy. The topical calcineurin inhibitors (eg, tacrolimus and pimecrolimus) offer additional advantages in the treatment of severe forms of AD,[8] but because some concerns on the safety were raised,[20] long-term surveillance studies are in progress.

Advances have been provided in the pathogenesis of AD, although the exact mechanism is still unclear. It has been shown that the priming response to allergens and or microbes is facilitated by IgE Langerhans cells and mast cells, as well as the chronic infiltration of skin-homing T_H2 memory T cells, and acute skin infiltrate results from a response driven by T_H2 cytokines (IL-4, IL-5, IL-13). On the contrary, in chronic AD, the T_H1 profile seems to be predominant, and cytokines such as IL-12, IL-18, IL-11, and TGF-β1 are involved.[21]

It is clear that, in some patients, AD has an allergic component. In fact, food allergens, bacteria, fungi, and aeroallergens,[2] especially HDMs may exacerbate AD. On the basis of this, it was hypothesized that SIT could exert a beneficial effect in AD. The results of the clinical trials with injection SIT are controversial. A double-blind controlled trial in 24 children failed to demonstrate the efficacy of HDM SIT after 8 months of treatment.[22] However, 6 additional months of therapy achieved a significant clinical improvement. Another study used intradermal injections of complexes containing autologous
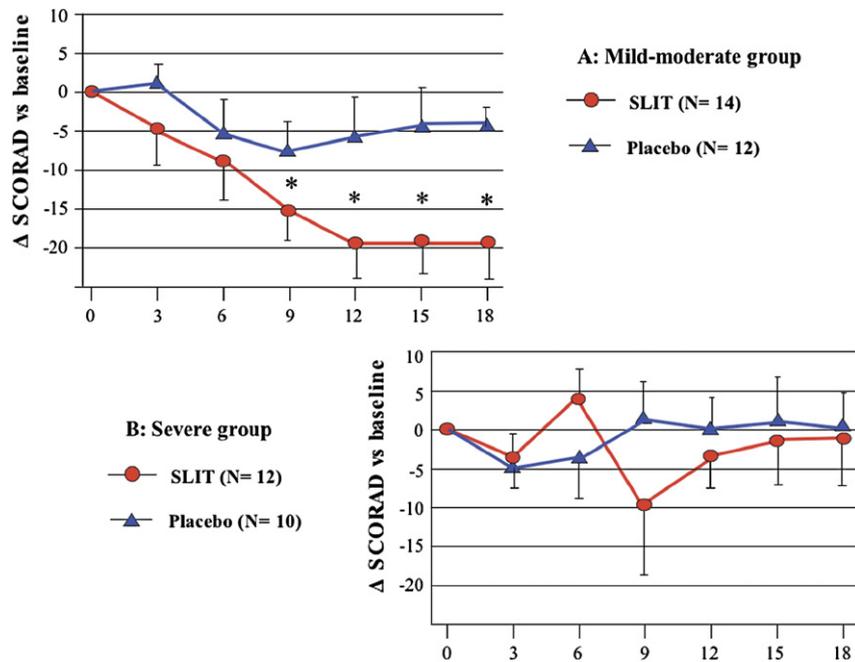
FIG 3. Change from baseline (Δ SCORAD) in the SLIT and placebo groups at the different time points. The patients are subdivided according to AD severity (**A,** mild-moderate; **B,** severe). *Significant differences.
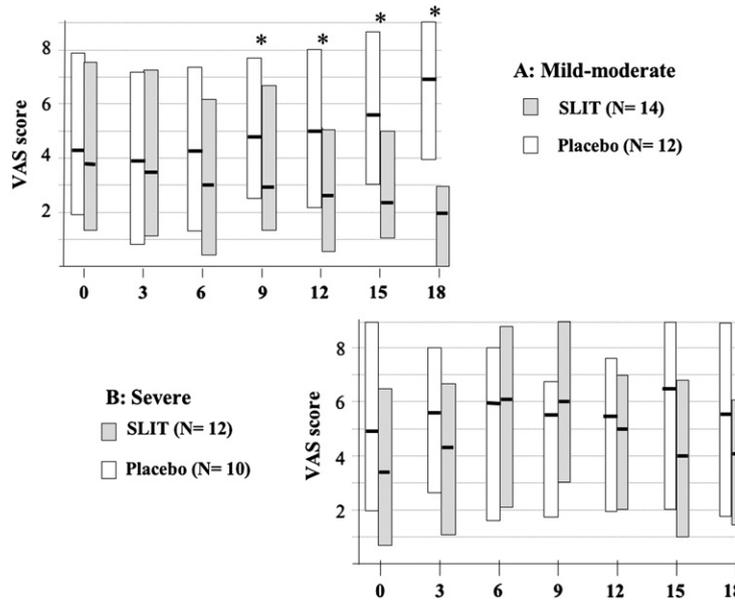

FIG 4. VAS scores (median, range) in the SLIT and placebo groups at the different time points. The *box* represents the range. The median is marked as a *thick line*. Patients are subdivided according to AD severity (**A,** mild-moderate; **B,** severe). *Significant differences.

specific antibodies and mite allergens[23] and demonstrated a relevant clinical improvement with measurable immunologic changes. An open and not controlled trial reported an improvement in erythema, lichenification, and respiratory symptoms in 32 children.[24] Finally, a recent randomized dose-response trial showed that injection HDM immunotherapy improved the eczema and reduced the need for topical steroids.[25] SLIT is currently accepted as a viable alternative to injections because of its satisfactory safety profile. Its efficacy in rhinitis in children has been confirmed in a recent meta-analysis,[14] but there are also favorable studies in pediatric asthma.[26,27] Despite its suitability in children, SLIT was poorly studied in AD. In 2 open controlled studies,[28,29] SLIT provided a significant
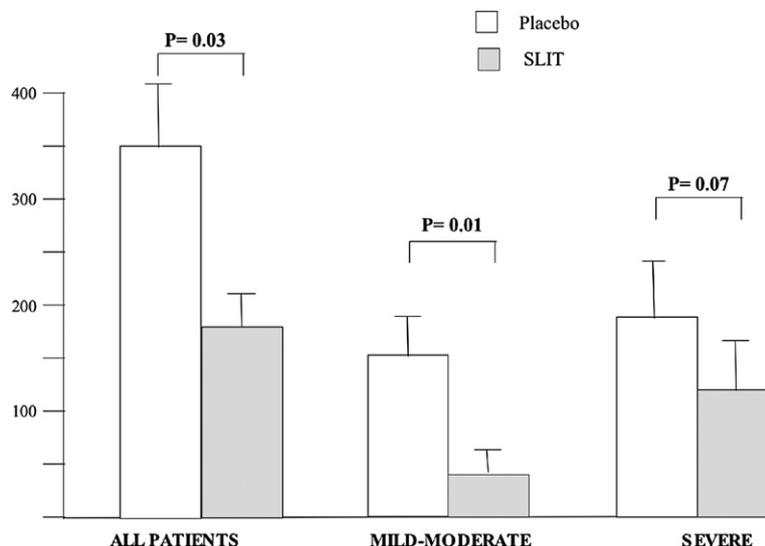
FIG 5. Total drug consumption (means, SEMs) in the whole population, in mild-moderate AD, and in severe AD.

improvement, whereas another trial with oral immunotherapy had previously given negative results.[30]

The current study was designed to assess whether SLIT displays any clinical efficacy in pediatric AD. SLIT proved effective in reducing eczema, as shown by the significant overall reduction of SCORAD index and medication intake. When the 2 severity subgroups were analyzed, patients with mild-moderate AD (SCORAD less than 40) did very well and showed an improvement of symptoms, drug scores, and VAS. On the other hand, in patients with severe AD, the benefits from SLIT were not significant. Looking at the VAS, a trend toward improvement was present, but it did not reach statistical significance. On the other hand, VAS is only a subjective and overall assessment of the disease in the last month, whereas SCORAD relies on objective aspects. In addition, the study was powered on SCORAD, and probably a larger sample would have been required to detect a change in the VAS. Of note, SLIT induced a relevant worsening of AD in 2 of the patients and had to be discontinued. This is consistent with the observations that in AD, the skin and mucosal contact with the allergen exacerbates the disease. This fact represents a possible limit of this treatment. Although the reactions were not life-threatening, we suggest that SLIT in AD be started under medical supervision. The double-blind randomized design was chosen to overcome the problems that occurred in the previous studies, mainly the open or uncontrolled design.[28-30] Another possible explanation for the clearly positive results, which differ from other studies, is the careful selection of the patients. In fact, we excluded subjects with food allergy or persistent asthma, which are confounding factors. In fact, food allergy could have confounded the clinical evaluation through exacerbation of cutaneous symptoms, and persistent asthma may have required the use of systemic corticosteroids. In addition, sensitization to HDM and high IgE levels were required to focus on the extrinsic form of AD. Finally, the treatment was given for as long as 18 months. In fact, in studies with HDM in respiratory allergy, a prolonged administration is required to observe a clinical effect.

We conclude that SLIT with a standardized mite extract can be considered effective in children with mild-moderate allergic AD, whereas the benefit was inconsistent in the severe form. This latter finding is similar to what is seen in asthma, in which SIT is less effective overall. The negative results achieved in patients with severe AD represent a stimulus for further clinical trials focusing on these patients.

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