



Letter

Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, open, parallel-group study

Allergen immunotherapy (AIT) is the only therapeutic approach that can modify the course of allergic diseases. Atopic dermatitis (AD) has an allergic component, but studies performed to assess the efficacy of AIT in AD are not yet conclusive.

The prevalence of atopic dermatitis (AD) and allergic diseases, such as rhinoconjunctivitis and asthma, is increasing in Western societies.¹ Several studies support the notion that pediatric patients with AD develop respiratory allergies during their lives (atopic march).^{1,2} In particular, house dust mites, such as *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, are mainly involved in this process.³

A recent meta-analysis provided moderate-level evidence of the efficacy of AIT in atopic dermatitis.⁴ The present study was designed to assess the efficacy of sublingual immunotherapy in house dust mite (HDM)–sensitized pediatric patients with AD, with or without associated allergic respiratory diseases. AIT was prolonged for 72 weeks because the efficacy of AIT with mite extracts requires a more prolonged treatment time compared with seasonal allergens.⁵

This was an open-label, six-center, randomized, controlled, phase 3b, parallel-group study. The treated group (group A) received sublingual immunotherapy (SLIT) with HDM standardized extracts in association with pharmacologic topical and/or systemic treatment on an as needed basis. The control group (group B) was treated with pharmacologic topical and/or systemic treatment on an as needed basis. The Investigational Medicinal Product was an extract of *D farinae* allergens (50%) and *D pteronyssinus* allergens (50%) for sublingual administration (SLITone; ALK-Abellò, Milan, Italy). Visits at the investigational study sites were performed at screening (visit 1, week –4), at baseline or start of treatment (visit 2, week 0), and after 4, 24, 48, and 72 weeks of treatment (visits 3, 4, 5, and 6, respectively). This study was evaluated and approved by the institutional review board of the ethic committee of each participating institution. Written informed consent was obtained from parents and/or guardians.

Diagnosis and main criteria for inclusion were as follows: (1) males and females older than 5 years and younger than 18 years; (2) patients with a clinical history of chronic mild to moderate AD,^{6,7} with no evidence of spontaneous remission at the age of 5 years, with or without intermittent moderate-severe or persistent mild-moderate rhinoconjunctivitis (in agreement with the Allergic Rhinitis and its Impact on Asthma criteria),⁸ or asthma⁹ not requiring regular use of inhaled corticosteroids; (3) sensitization to *D pteronyssinus* and/or *D farinae* diagnosed by prick test (wheal

diameter >3 mm) and by specific serum IgE (class III or higher according to ImmunoCAP, ThermoFisher Scientific Inc., Phadia AB, Uppsala, Sweden); (4) positive atopy patch test result to house dust mite extracts¹⁰ (a concomitant sensitization to pollen allergens was acceptable, provided that there were no exacerbations of AD during pollination); and (5) Scoring Atopic Dermatitis (SCORAD) scores⁶ greater than 8 but 40 or less.

The primary efficacy end point was the change of SCORAD score⁶ from baseline to any postbaseline time point. The secondary objectives of the study were to assess (1) changes of subjective perception of cutaneous symptoms (visual analog score on a 0–10 scale, where 0 was no symptoms and 10 was maximum of symptoms) from baseline to any postbaseline time point and (2) investigator judgment on efficacy from baseline to any postbaseline time point. Investigator judgment on disease activity was categorized at each time point as follows: worsened, unchanged, improved, or much improved. Further details on methods are reported in the eMethods.

We found that in the intent-to-treat population, the mean SCORAD total score decreased from baseline to any postbaseline time point in the SLIT group, compared with small decreases from baseline to weeks 4, 24, and 72, and no substantial changes at week 48 in the control group (Fig 1). The mean (SD) change from baseline to the final visit (week 72) was –11.9 (22.38) in the SLIT group and –2.78 (15.44) in the control group. The comparison between groups of changes from baseline revealed statistically significant differences in favor of the SLIT group at week 48 ($P = .02$) and at week 72 ($P = .02$), whereas the difference between groups at week 4 and week 24 was not statistically significant. The results in the per patient population were consistent with those observed in the intent-to-treat population.

The mean VAS score of symptoms decreased from baseline to any postbaseline time point in both groups. The mean (SD) change from baseline to the final visit (week 72) was –2.48 (3.481) in the SLIT group and –1.77 (3.054) in the control group.

Finally, the results of the investigator's judgment of efficacy revealed a more favorable investigator's judgment for SLIT than for standard therapy. The comparison between groups revealed a statistically significant difference ($P = .02$) in favor of the SLIT group.

Eight adverse events were reported in 5 patients (16.7%) in the SLIT group and 2 adverse events were reported in 2 patients (7.4%) in the control group. The adverse events in the SLIT group consisted of immediate and transient local events. The adverse events in the control group consisted of consent withdrawn in both cases. Four serious adverse events occurred in 1 patient in the control group (3 episodes of staphylococcal infection and 1 episode of asthma). Further details on results are reported in the eResults.

In conclusion, we found that in a pediatric population with AD and HDM sensitization, a 72-week course of sublingual AIT with a

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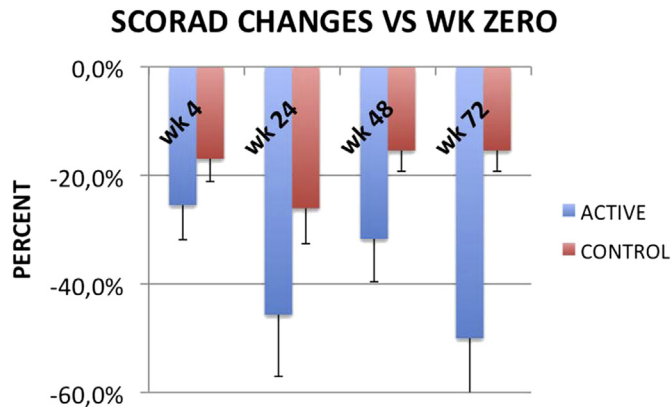


Figure 1. Scoring Atopic Dermatitis (SCORAD) total score changes vs baseline in the intent-to-treat population. SCORAD total scores are indicated on the y-axis as the percentage of median values vs baseline median values at different time points since study start (weeks, on the x-axis). The sublingual immunotherapy group values (active in legend, blue) and control group values (red) are represented as paired columns at each considered time point.

standardized mite extract significantly reduced the primary variable SCORAD total score compared with standard treatment. Treatment with SLIT was well tolerated, and few patients reported immediate and transient local reactions.

The main limit of this study was the absence of blinding, which may have influenced investigators and patients' perception of study results. Double-blind, placebo-controlled studies on larger cohorts of patients are needed to assess the efficacy of SLIT in pediatric patients with AD, with or without associated allergic respiratory diseases and HDM sensitization.

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eMethods

Demographic characteristics of patients and diagnosis at screening are reported in eTables 1 and 2.

eResults

SCORAD Total Score Change

In the ITT population, the mean SCORAD total score decreased from baseline to any postbaseline time point in the SLITone group, compared to small decreases from baseline to week 4, 24 and 72, and no substantial changes at week 48, in the control group. The mean ($\pm$ SD) change from baseline to the final visit (week 72) was -11.9 ± 22.38 in the SLITone group and -2.78 ± 15.44 in the control group. The comparison between groups of changes from baseline showed statistically significant differences, in favor of the SLITone group, at week 48 ($P = .021$) and at week 72 ($P = .016$), whereas the difference between groups at week 4 and at week 24 was not statistically significant. The results in the PP population were consistent with those observed in the ITT population.

Subjective Perception and Investigator Judgment on Efficacy

The mean VAS score of symptoms decreased from baseline to any postbaseline time point in both groups. The extent of the decrease was more marked in the control group than in the SLITone group at week 4 and week 24, whereas was it more marked in the SLITone group than in the control group at week 48 and week 72. The mean ($\pm$ SD) change from baseline to the final visit (week 72) was -2.48 ± 3.481 in the SLITone group and -1.77 ± 3.054 in the control group. The comparison between groups of changes from baseline did not show statistically significant differences at any postbaseline time point. The results of Investigator's judgment of efficacy showed a more favorable Investigator's judgment for SLITone than for standard therapy. In the SLITone group, 9 patients (39.13%) were considered as much improved, 11 (47.83%) as improved and 3 (13.04%) as unchanged. In the Control group, 1 patient (6.67%) was considered as much improved, 8 (53.33%) as improved, 2 (13.33%) as unchanged and 4 (26.67%) as worsened. The comparison between groups showed a statistically significant difference ($P = .02$), in favor of the SLITone group.

eTable 1
Demographic characteristics of patients (randomized population)

	SLITone group (n=30)	Control group (n=27)
Sex		
Female	11 (36.67%)	10 (37.04%)
Male	19 (63.33%)	17 (62.96%)
Race		
Caucasian	26 (86.66%)	25 (92.59%)
African	1 (3.33%)	-
Asian	3 (10.00%)	1 (3.70%)
Other	-	1 (3.70%)
Age (years)		
Mean	11.27	11.23
SD	4.19	4.69
SE	0.76	0.90
Median	11.18	11.75

eTable 2
Diagnosis at screening and severity of the disease (randomized population)

	SLITone group (n=30)	Control group (n=27)
Symptomatology		
Atopic Dermatitis only	8 (26.67%)	8 (29.63%)
A. Dermatitis + Rhinitis	8 (26.67%)	9 (33.33%)
A. Dermatitis + Conjunctivitis	1 (3.33%)	-
A. Dermatitis + Conjunctivitis + Rhinitis	4 (13.33%)	3 (11.11%)
A. Dermatitis + Asthma	1 (3.33%)	2 (7.41%)
A. Dermatitis + Rhinitis + Asthma	4 (13.33%)	2 (7.41%)
A. Dermatitis + Conjunctivitis + Rhinitis + Asthma	3 (10.00%)	3 (11.11%)
A. Dermatitis + Rhinitis + Other	1 (3.33%)	-
Atopic Dermatitis	30 (100.00%)	27 (100.00%)
Rhinitis	20 (66.67%)	17 (62.96%)
ARIA classification		
Mild - Intermittent	4 (20.00%)	3 (17.65%)
Mild - Persistent	8 (40.00%)	7 (41.18%)
Moderate/severe - Intermittent	3 (15.00%)	3 (17.65%)
Moderate/Severe - Persistent	5 (25.00%)	4 (23.53%)
Conjunctivitis	8 (26.67%)	6 (22.22%)
Asthma	8 (26.67%)	7 (25.93%)
GINA classification		
Intermittent	8 (100.00%)	3 (42.86%)
Mild - Persistent	-	1 (14.28%)
Moderate - Persistent	-	3 (42.86%)
Other (previous intolerance to milk protein)	1 (3.33%)	-