

Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures

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Although several studies have demonstrated the efficacy of subcutaneous immunotherapy in allergic asthma, few have shown the same benefit using sublingual immunotherapy (SLIT) in asthmatic patients. This study was conducted to assess the efficacy of house dust mite (HDM) SLIT in addition to allergen avoidance and standard pharmacologic treatment. A double-blind, placebo-controlled trial was performed in 111 children (aged 5–15 yr) with HDM-induced mild-to-moderate asthma. After a 4-week baseline phase, patients were randomly assigned to receive SLIT with tablets of HDM extract ($n = 55$) or placebo ($n = 56$) for 18 months. Pharmacologic treatment was adjusted every 3 months following a step-down approach. Asthma symptom scores, reduction in use of inhaled corticosteroids and inhaled β_2 -agonists, rhinitis symptoms, lung function tests, skin sensitivity to HDM, dust mite-specific immunoglobulin (Ig) E and IgG₄, and quality of life (QoL) were assessed during the study. After 18 months of treatment, diurnal and nocturnal asthma symptoms scores did not show significant differences between SLIT and placebo groups. Inhaled corticosteroids and inhaled β_2 -agonists use was reduced in both groups without significant differences between groups. There were no significant differences in lung function (forced expiratory volume in 1 s and peak flow rate variations) between groups. Rhinitis symptom score decreased in both groups, with no difference between the two groups. The severity dimension of QoL was significantly improved in the SLIT group (age 6–12 yr). SLIT induced a significant reduction of skin sensitivity to HDM ($p < 0.01$) and a significant increase in HDM-specific IgE and IgG₄ antibodies ($p < 0.001$) in the SLIT group compared with the placebo group. SLIT was well tolerated with mild/moderate local adverse events. No severe systemic reactions were reported. This study indicates that, when mild–moderate asthmatic children are optimally controlled by pharmacologic treatment and HDM avoidance, SLIT does not provide additional benefit, despite a significant reduction in allergic response to HDM. Under such conditions, only a complete, but ethically unfeasible, discontinuation of inhaled corticosteroid would have demonstrated a possible benefit of SLIT.

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Allergic asthma is a common pathology in children, and house dust mite (HDM) is the most frequent indoor allergen implicated in this condition (1). The management of allergic asthma has been defined in the Global Initiative for Asthma (GINA) guidelines, which recommends the association of allergen avoidance, pharmacologic treatment and allergen immunotherapy when indicated (2). In asthmatic adults and children sensitized to HDM, specific immunotherapy (SIT) has been shown to be effective in reducing asthmatic symptoms, medications use, and specific and non-specific bronchial hyper-responsiveness (3–6). Moreover, it has recently been shown that SIT can be used to prevent the appearance of new sensitivities to airborne allergens in children exclusively sensitized to HDM (7, 8). Nevertheless, subcutaneous administration of SIT is inconvenient and is occasionally associated with severe systemic side effects despite the guidelines developed for its use (9). To overcome these disadvantages, sublingual immunotherapy (SLIT), which has been developed over the past 15 yr, offers a better safety profile and ease of use. These advantages makes it a strongly attractive option for children (10–12).

The efficacy of SLIT in allergic rhinitis has been reviewed recently in a Cochrane meta-analysis of 22 studies (13), which concluded that it had significant efficacy in pollen-induced rhinitis but less significant efficacy in HDM-induced rhinitis. In addition, a recent well-designed, controlled study comparing SLIT and subcutaneous immunotherapy in patients with allergic rhinitis showed no difference in efficacy between the two routes (14).

In comparison with allergic rhinitis, only six controlled studies have been performed to assess the efficacy of SLIT in allergic asthma, particularly in children sensitized to HDM (15–20). These trials have shown that, in comparison with placebo, SLIT for HDM sensitivity could provide protection against the relevant allergen, reduce symptoms, reduce medication intake, and improve lung function. However, the drawback of these studies was the lack of adjustment for pharmacologic treatment, and poor implementation of allergen-avoidance strategies. Given that SIT acts on both immunologic and inflammatory response of allergic disease (21, 22), it is tempting to argue that SIT could be a complementary treatment to symptomatic drugs in asthma. Inhaled corticosteroids are widely accepted as the cornerstone treatment of asthma (2). However, concern about their long-term safety has led to the use of add-on therapies

to minimize inhaled corticosteroids exposure according to a 'step-down' approach (23–25). The step-down asthma therapy approach including SLIT has not been extensively studied. The aim of this study was to establish whether SLIT might be a useful add-on treatment for asthmatic children allergic to HDM and receiving appropriate medical treatment, including standard HDM avoidance and pharmacologic treatment in line with the GINA guidelines.

Materials and methods

Patients

One hundred and 11 asthmatic children aged 5–16 yr were recruited at the outpatient clinic of the study group's investigators. The subjects, who were already known to their physicians, had to fulfill the following criteria:

- 1 have asthma, with or without perennial rhinitis, for at least 2 yr, be receiving treatment with an inhaled corticosteroid (>200 and ≤ 1000 $\mu\text{g/day}$ /equivalent budesonide) daily and continuously for at least 6 months during the previous 12 months;
- 2 have reversible bronchial obstruction, as assessed by salbutamol inhalation test [increase in forced expiratory volume in 1 s (FEV_1) of $\geq 15\%$ after inhaled salbutamol] during the past 2 yr;
- 3 be sensitized to dust mites, as proved by positive skin tests to HDM extract (Stallergenes, Antony, France) and be HDM-specific immunoglobulin (Ig) E level greater than or equal to class 2 (CAP RAST) (Pharmacia, Uppsala, Sweden).

Exclusion criteria were:

- 1 concomitant sensitization to perennial allergens such as cockroach, *Alternaria* or *Cladosporium* mold species, cat, dog (if animal at home), and to seasonal pollen allergens inducing allergic symptoms lasting longer than 4 months/yr. Sensitizations were based on a clear-cut clinical history, positive skin tests and specific IgE (CAP RAST greater than or equal to class 2).
- 2 Previous immunotherapy with HDM extracts within 3 yr from the date of inclusion;
- 3 contraindications to SIT, according to the international guidelines (9).

The study was approved by the ethical committee of the Hospital Pitié-Salpêtrière in Paris, and the

participants and their parents written consent was obtained. The study was performed according to ICH-GCP guidelines.

Study design

We performed a randomized, double-blind, placebo-controlled study. Children were recruited over 4 months and underwent a 4-wk run-in period before randomization, during which they were assessed for asthma severity and to ensure they met the inclusion criteria. The children were then randomized 1:1 to receive SLIT or placebo with a stratification based on inhaled corticosteroid daily intake. Treatment duration was for 18 months from November 2000 to May 2002 (Fig. 1).

Primary endpoint was the asthma symptom score (nocturnal and diurnal) and the number of asthma-free days (when diurnal + nocturnal score = 0). Secondary endpoints were the asthma medication score (use of rescue medication), assessment of lung function parameters [FEV₁, peak expiratory flow rate (PEFR), quality of life (QoL), rhinitis symptoms scores, skin-prick tests (SPTs), total and specific IgE and IgG₄ antibodies].

Assessment of dust mite exposure and avoidance measures

At the investigators' request an environmental consultant performed a first home visit for each patient during the baseline period. The consultants recommended that the patients' bedrooms were cleaned adequately, which included carpet cleaning and regular washing of teddy bears. Then patients' mattresses were vacuumed using a standardized technique to collect dust samples. The samples were stored at 4°C in sealed paper vacuum bag and sent to a central

laboratory for HDM major allergen (Der p 1) determination. At the end of this first visit, antimite mattress and pillow covers (ACB; Medeca AB, Uppsala, Sweden) were provided to all patients and placed by the consultant on each patient's bed. Where patients already had antimite covers, these were replaced by new ones. The same consultant repeated the dust sampling after 12 and 18 months of treatment. The dust concentration of major allergen Der p 1 (expressed as micrograms of Der p1 per gram of dust) was assayed according to the method described previously (26).

SLIT

Patients in the active group were treated with tablets of allergen extract consisting of a 1:1 mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Stallergenes) prepared and standardized according to a method described previously (27). The biologic activity of the extract was expressed in Index of Reactivity (IR). A potency of 100 IR was designated as the strength of HDM extract that elicited a geometric mean wheal size of 7-mm diameter by SPT in 30 subjects who were sensitive to the corresponding allergen. A tablet at a concentration of 100 IR contained 9 µg Der p1 and 19 µg Der f 1, which is the major *D. farinae* allergen. Four concentrations were used in the study: 10, 30, 100 and 300 IR. Placebo tablets were identical to the active extract in appearance, presentation, taste and colour. A 2-wk up-dosing phase of SLIT was applied, beginning with the 10 IR concentration (one tablet on days 1 and 2, two tablets on days 3 and 4), then 30 IR concentration (one tablet on days 5 and 6, two tablets on days 7 and 8), then 100 IR concentration (one tablet on days 9–11, two tablets on days 12–14)

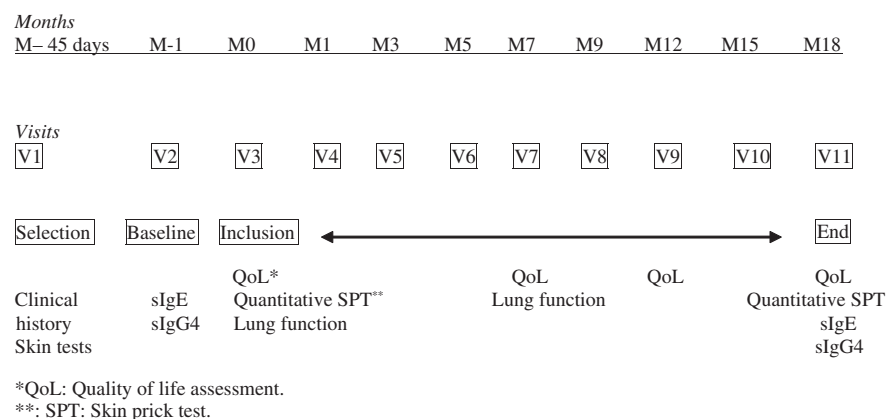


Fig. 1. Study flow chart.

until the 300 IR final concentration (one tablet on day 15). The maintenance dose remained at one 300 IR tablet daily, for the remaining 17 and a half months of the study. The average cumulative dose taken by the patients was 155,000 IR, corresponding to 6.9 mg Der p 1 and 14.7 mg Der f 1. Children were instructed to place the tablets under the tongue and to keep them there until dissolved before swallowing. An assessment of patient compliance was made at each visit by the investigator and was based on the frequency and duration of temporary interruptions of treatment.

Symptom score and rescue medication use

Patients were asked to keep a daily record of their symptoms and a record of rescue medication use during the baseline period and for 3 wk before each visit. Nocturnal and diurnal asthma symptoms were recorded on a four-point scale (0–3, with 0 indicating no symptoms and 3 indicating severe symptoms). Daily average asthma scores were calculated as the arithmetic mean values of daily scores during the past 21 days of each diary card. Asthma scores and percentage of asthma-free days were calculated from baseline, each intermediate visit and at study endpoint (data from the previous 3 wk of the last diary card). Rhinitis symptoms (sneezing, rhinorrhea, nasal blockade, and nasal itching) were recorded as a global score on the same diary card. This global score was rated on a four-point scale, with 0, no symptoms; 1, one or several rhinitis symptoms are present but not disturbing; 2, one or several rhinitis symptoms are present and disturbing; and 3, one or several rhinitis symptoms are present and severe.

Terbutaline [metered-dose inhaler (MDI), 250 µg per actuation] was used as a short-acting bronchodilator. Budesonide (MDI, 100 or 200 µg per actuation) was used as a regulatory inhaled steroid. In case of asthma exacerbation, the investigator prescribed a short course of prednisolone (20 mg per tablet). No other anti-asthma drugs were allowed. Intake of antiasthma drugs was recorded as the number of puffs per day. We planned a three-stage, step-down approach to achieve a minimum dose of inhaled corticosteroid. The step-down (backward titration) of dose occurred at visit 6 (i.e. 5 months after the start of treatment), at visit 8 (after 9 months of treatment), and at visit 9 (V9) (after 12 months). The dosage of inhaled corticosteroids was reduced by 20–30% at each stage, based on the asthma symptom severity, PEFR variability, and FEV₁ values.

To treat rhinitis symptoms, patients were allowed to use an oral antihistamine (cetirizine tablets or loratadine tablets or syrup). Intake of antihistamines was recorded as the number of tablets or spoonfuls per day. Medication intake at baseline and at endpoint were determined.

Lung function measurements

Patients were supplied with peak flow meters (Mini-Wright, Clement Clarke, UK) and were requested to measure and report on their diary card morning and evening PEFR during the run-in period and in the 3-wk period before each visit. PEFR variability (%) between morning and nighttime values was calculated by the investigator for each of the 7 days preceding each visit. Lung function tests were performed at each visit using a dry spirometer. Subjects were advised to avoid the use of the short-acting bronchodilator at least 12 h before the test. FEV₁ values were expressed as a percentage of predicted values. PEFR and FEV₁ at inclusion visit and at the final visit were determined.

Quality of life assessment

Quality of life was assessed using two forms of the Childhood Asthma Questionnaire (CAQ) developed by Christie et al. (28). The form CAC-B, which was used for 6- to 11-yr-old children, comprises 21 items grouped into four dimensions. This form assesses children's perceptions of the active and passive aspects of living with asthma, and their perceptions of severity and the associated distress. The questionnaire was completed by children or by parents if the child could not read easily. The form CAC-C, which was used for 12- to 16-yr-old children, comprises 39 items grouped into five dimensions: distress, severity, reactivity, active quality of living and teenage quality of living. Scoring of the CAQ questionnaires were derived by totalling the score of the items indicated. The higher the score the stronger the patient experienced the concept covered by that dimension. The CAQ questionnaires were administered at baseline (V3), V7, V9 and V11.

Skin tests

Quantitative SPTs were performed at the end of the baseline period and at the end of the study (V11). SPTs were performed in duplicate using a *D. pteronyssinus* extract (Stallergenes SA) at five concentrations: 2, 6, 18, 55, and 166 IR/ml. Codeine phosphate was used as positive control

and 0.9% glycerol-saline solution as negative control. Skin reactions were recorded after 15 min. The wheal reaction was outlined and transferred with a transparent adhesive tape onto a record sheet. The mean wheal diameter was recorded. Results were expressed as changes from V3 to V11 of a theoretical wheal diameter with 100 IR/ml concentration.

Immunologic parameters

Blood samples were taken before treatment, after 12 months, and at the end of the study for specific *D. pteronyssinus* and *D. farinae* IgE and IgG₄ antibody assays. All analyses were performed at the end of the trial in a central laboratory using the CAP System[®] (Pharmacia). Results were expressed in kIU/l for specific IgE and $\mu\text{g/l}$ for IgG₄.

Statistical analysis

A placebo effect of 30% (meaning that the symptom score improves by 30% in the placebo group) and an improvement of symptoms with SLIT of around 60% was assumed for the determination of the sample size. To demonstrate a difference between the two groups on the percentage expected with a risk $\alpha = \beta = 5\%$, 70 subjects in each group would be required. The primary efficacy criteria (diurnal and nocturnal asthma scores) were change of asthma scores and proportion of asthma-free days from baseline to endpoint. Quantitative data are presented as

mean values and, when data were non-Gaussian, they were expressed as median values with first and third quartiles (Q1 and Q3). The Mann-Whitney *U*-test was used for between-group comparisons. For intragroup comparisons the Wilcoxon two-sample test was used. A group comparison for FEV₁ time trend was performed using two-way analysis of variance (ANOVA). For qualitative data, the two groups were compared using the Mantel-Haenszel chi-squared tests or Fisher's exact probability if the theoretical numbers were low. The statistical tests were performed as two-sided tests with a significance level $\alpha = 0.05$. All statistical analyses were performed using SAS 6.12 (SAS Inst., Cary, NC, USA).

Results

Patients

One hundred and sixteen patients were screened. All patients were well known to their physicians, who had managed them for many years. Few patients were lost between screening and randomization due to their parents' willingness to participate in the clinical trial and the subsequent good compliance.

Of the 111 children randomized, 19 dropped out before the study completion (eight in the placebo group and 11 in the SLIT group); thus 44 patients with SLIT and 48 patients with placebo completed the study. The reasons for dropout are shown in Fig. 2. Among the 19 patients who withdrew, 10 in

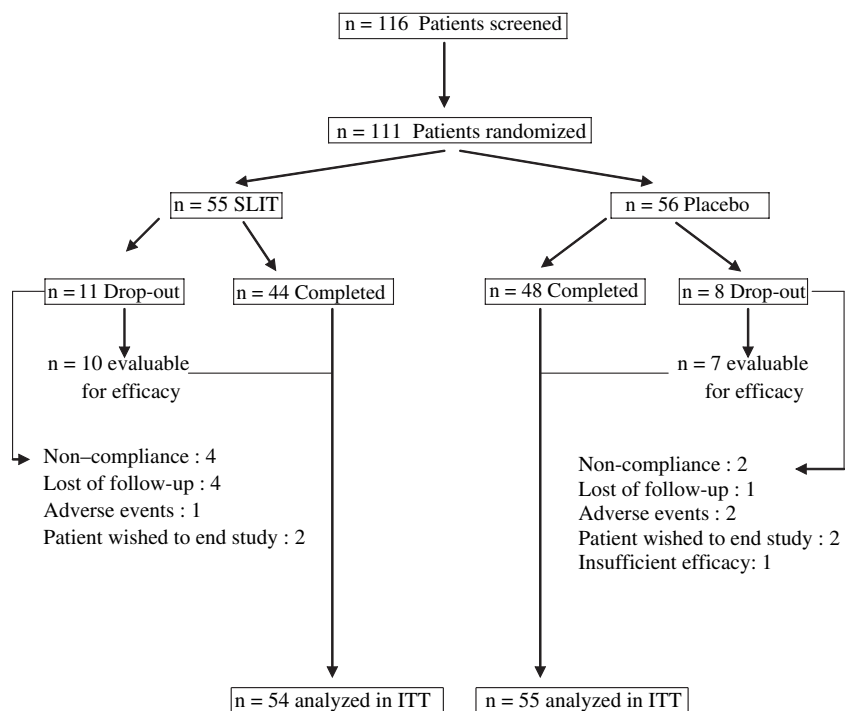


Fig. 2. Study profile.

the SLIT group and seven in the placebo group were considered evaluable for the intent-to-treat analysis (ITT), which included 54 patients in the SLIT group and 55 patients in the placebo group. However, the target of 70 patients per treatment arm completing the study as statistically planned for the sample size could not be reached.

The baseline characteristics of the patients included in the ITT analysis are reported in Table 1. At baseline there were no statistically significant differences between the two groups for any of the variables listed. Of the 109 patients, 73 patients were graded as having mild asthma and 36 had moderate asthma. Asthma symptom scores before treatment were very low (median values were close to 0 on a 0–3 scale), indicating that half of the patients had no symptoms of asthma during the baseline period, consequently, the proportion of days without asthma was very high (median values for all patients = 90.5%), and the intake of β_2 -agonists was very low.

The average dropout rate because of non-compliance was 20% and the frequency of temporary treatment interruption was very low (data not shown).

Symptom and medication scores

After 18 months of treatment, diurnal and nocturnal asthma symptom scores, already very low at

baseline were slightly reduced in both groups without significant differences (Table 2). Taking into account the very low symptom scores reported before treatment, the values for changes from baseline were close to zero. Consequently, the percentage of asthma-free days, despite a slight increase at the end of the study, did not show any statistically significant difference between the groups. Because asthma symptoms were almost absent, the planned step-down reduction of inhaled corticosteroids was possible. Thus, inhaled corticosteroid intake was reduced by 53% in the SLIT group and 61% in the placebo group (mean values). The percentage change of inhaled corticosteroids intake from baseline at endpoint did not differ significantly between treatment groups (Table 2). The same pattern was observed for β_2 -agonist use. Because intake was very low at baseline, the change from baseline to endpoint was negligible. Diurnal and nocturnal intake of terbutaline did not differ significantly between the groups. Analysis of the two subgroups stratified on initial asthma severity (both mild and moderate) did not modify the outcome of the study. Few variations of lung function parameters were observed (Table 2). FEV₁ values showed an average decrease of –3.32% in the SLIT and –0.9% in

Table 1. Baseline characteristics of children included in the study

Parameters	SLIT group (n = 54)	Placebo group (n = 55)
Age, mean (range) (yr)	9.6 (5–14)	9.5 (5–16)
Sex, M/F	39/15	39/16
Asthma duration (yr)*	6.1 ± 5	5.7 ± 4
Asthma severity, n (%)		
Mild†	35 (65)	38 (69)
Moderate	19 (35)	17 (31)
Perennial rhinitis, n (%)	44 (81)	43 (78)
Grass-pollen allergy, n (%)	13 (24)	19 (34)
Skin tests, wheal diameter‡		
<i>Dermatophagoides</i>	5.9 (4.9–7.5)	6 (4.4–7.9)
<i>pteronysinus</i> wheal (mm)		
<i>Dermatophagoides</i>	5.7 (4.7–7.2)	6.5 (4.8–7.9)
<i>farinae</i> wheal (mm)		
FEV ₁ (% predicted)*	91.9 ± 13.4	95.1 ± 15.1

SLIT, sublingual immunotherapy; FEV₁, forced expiratory volume in 1 s.

*Values given are mean ± s.d.

†Mild persistent asthma [Global Initiative for Asthma (GINA) step 2] is characterized by daily symptoms greater than or equal to once a week but less than once a day, treated by daily inhaled corticosteroids inhaled (>200 and ≤ 500 µg/day equivalent budesonide) and short- or long-acting inhaled β_2 -agonists. Moderate persistent asthma (GINA step 3) is characterized by daily symptoms with nocturnal asthma less than once a week but less than once a day, treated by daily inhaled corticosteroids (>500 and ≤ 1000 µg/day) daily and short- or long-acting inhaled β_2 -agonists.

‡Skin tests performed at visit 1 before the baseline period. The data are presented as median wheal size (interquartile range).

Table 2. Symptoms scores, medication intake and lung function parameters at baseline and at SLIT endpoint

	SLIT (n = 54), mean ± s.d.	Placebo (n = 55), mean ± s.d.	p-value*
Diurnal asthma			
Baseline	0.19 ± 0.30	0.17 ± 0.24	
Endpoint	0.15 ± 0.26	0.08 ± 0.17	NS
Nocturnal asthma			
Baseline	0.17 ± 0.30	0.11 ± 0.18	
Endpoint	0.10 ± 0.19	0.07 ± 0.16	NS
% asthma-free days			
Baseline	78.5 ± 27.4	80.8 ± 23.8	
Endpoint	85.8 ± 23.8	91.1 ± 15.4	NS
Use of inhaled steroids (µg budesonide/day)			
Baseline	548 ± 220	534 ± 237	
Endpoint	257 ± 232	223 ± 270	NS
Use of inhaled β_2 -agonists (terbutaline puffs/day)			
Baseline	0.87 ± 0.5	0.90 ± 0.8	
Endpoint	0.55 ± 0.6	0.47 ± 0.5	NS
Rhinitis daily score			
Baseline	0.71 ± 0.76	0.50 ± 0.58	
Endpoint	0.12 ± 0.14	0.17 ± 0.19	NS
PEFR variability (%)			
Baseline	8.03 ± 7.21	7.48 ± 6.14	
Endpoint	6.06 ± 5.45	6.36 ± 5.65	NS
FEV ₁ (% predicted value)			
Baseline	91.9 ± 13.4	95.1 ± 15.1	
Endpoint	88.5 ± 13.4	94.5 ± 14.6	NS

SLIT, sublingual immunotherapy; PEFR, peak expiratory flow rate; FEV₁, forced expiratory volume in 1 s;

*Level of significance for between-group differences; NS, not significant.

the placebo group. In both groups, this study showed a reduction of PEFR variability from baseline to the last visit. For all parameters no significant differences were detected between the two groups. As a secondary efficacy outcome, rhinitis symptoms score decreased significantly in both groups, until an almost complete suppression of symptoms, but with no statistically significant differences between the groups (Table 2).

Quality of life

More than 90% of the CAC-B and CAC-C questionnaires received were assessable. In the CAC-B population (age 6–11 yr, $n = 82$), 20% of the patients had the maximum QoL score at inclusion for passive activities dimension. During the trial the severity dimension showed a significant improvement in the SLIT group compared with the placebo group ($p = 0.04$). In the CAC-C population (age 12–16 yr, $n = 29$), 14% of the patients had a maximum QoL score for reactivity dimension. In both SLIT and placebo groups, the average changes in all dimensions were comparable and no statistically significant between-group differences were observed.

Skin tests

Immediate skin reactivity to *D. pteronyssinus* extract decreased significantly from the beginning to the end of treatment in the SLIT group in comparison with the placebo group ($p < 0.010$) (Table 3). The median skin wheal diameters for *D. pteronyssinus* at 100 IR/ml concentration were reduced by 45.2% in the SLIT group ($p < 0.001$ intragroup comparison) whereas there was a 8.7% reduction (non-significant) in the placebo group.

Immunologic parameters

The results of serum analyses for specific IgE and IgG₄ are shown in Fig. 3. We found a significant increase of mean *D. pteronyssinus*-specific IgE levels from 208 ± 38 kIU/l at baseline to

282 ± 40 kIU/l at 12 months and 250 ± 36 kIU/l at 18 months for the SLIT-treated patients, whereas specific IgE levels decreased in the placebo group (from 197 ± 30 kIU/l at baseline to 135 ± 21 kIU/l at 18 months). The difference between the two groups was significant ($p < 0.001$).

In the SLIT group, *D. pteronyssinus*-specific IgG₄ increased from 1166 ± 188 µg/l (mean $\pm$ SE) before SLIT to 3869 ± 769 µg/l after 12 months of treatment and to 4462 ± 860 µg/l at the last follow-up visit. In the placebo group, *D. pteronyssinus*-specific IgG₄ levels did not change significantly (761 ± 73 µg/l at baseline, 763 ± 135 µg/l after 12 months and 650 ± 51 µg/l at the last follow-up visit). On average, the levels of *D. pteronyssinus*-specific IgG₄ antibodies in the SLIT group at the last follow-up visit were 3.8 times higher than the baseline values, however, IgG₄ antibodies were unchanged in the placebo group over this period ($p < 0.001$). Similar patterns were observed for *D. farinae*-specific IgE and IgG₄ antibodies levels in both groups (data not shown).

Dust-mite exposure

At baseline the content of Der p1 allergens in the bedroom dust of subjects' houses was comparable in both groups (median value = 3.54 µg/g dust for SLIT group vs. 3.71 µg/g in placebo group). At 12 months the average concentrations decreased similarly in the two groups (2.86 µg/g dust for SLIT group vs. 2.32 µg/g in placebo group). At 18 months the amount of Der p1 increased slightly in the SLIT group (3.10 µg/g) and decreased again in the placebo group (1.18 µg/g). None of these differences were statistically significant.

Safety assessment

Adverse events are shown in Table 4. Adverse events related to the study treatment occurred at least once in 39 of 55 (71%) patients treated with SLIT and 37 of 56 (66%) placebo-treated

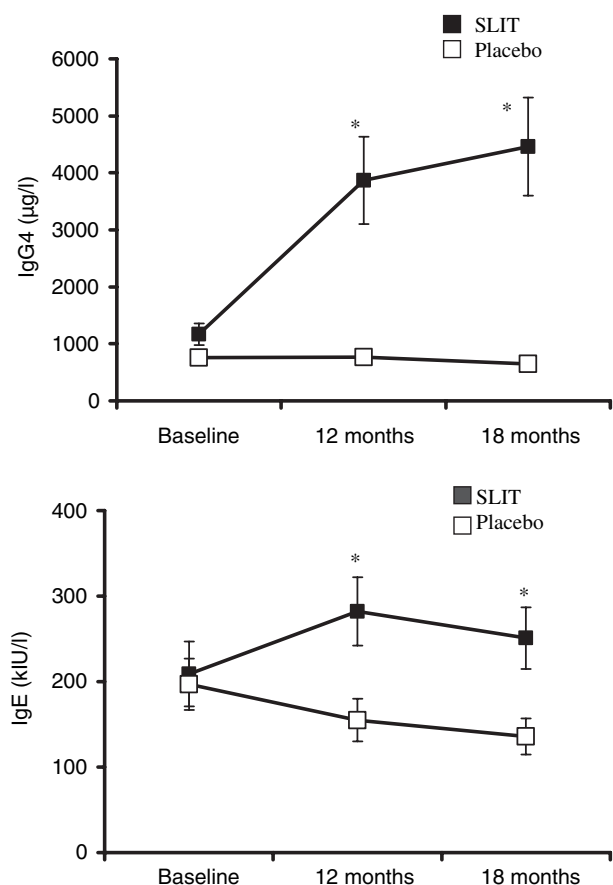
Table 3. Skin-prick tests responses to *Dermatophagoides pteronyssinus* at baseline (V3) and at the end of the study (V11)

	SLIT		Placebo	
	V3	V11	V3	V11
Skin wheal diameter (mm) (interquartile ranges)	5.31 (3.96–7.55)	2.90 (0.36–4.45)*	5.81 (4.10–7.13)	5.30 (0.90–8.10)
Median changes V3–V11 (mm) (min–max)		–2.15 (–10.2 to 4.6)		–0.46 (–15.6 to 23.8)

Data are presented as median of a theoretical wheal diameter obtained with a 100 IR/ml concentration.

SLIT, sublingual immunotherapy.

*Between-group differences: $p = 0.010$.



* Level of significance for between-group differences: $p < 0.001$

Fig. 3. *Dermatophagoides pteronyssinus*-specific immunoglobulin (Ig)G4 and IgE antibodies levels (mean $\pm$ SEM) at baseline (V3), after 12 months (V9) and after 18 months (V11) of treatment. *Level of significance for between-group differences, $p < 0.001$.

Table 4. Adverse events

Adverse event	SLIT (n = 55)	Placebo (n = 56)
Respiratory (rhinitis and/or asthma)	64	67
Gastrointestinal complaints	19	2
Mouth itching/lip swelling	10	5
Total no. adverse events	93	77
No. patients who experienced at least one adverse event	39 (71%)	37 (66%)*

SLIT, sublingual immunotherapy.

* $p = 0.58$ (chi-squared test). The percentage of patients with at least one adverse event did not differ significantly between treatment groups. Statistical analysis of adverse events was descriptive. No inferential analysis was performed except the comparison of the two treatment groups on the proportion of patients with at least one adverse event using a chi-squared test.

patients. Local oral and gastro-intestinal reactions occurred more frequently in SLIT-treated group. Some adverse events were effectively treated by either dose reduction or/and antihistamines. Gastrointestinal complaints led to one

patient's withdrawal in each group. One patient in the placebo group withdrew after a severe acute exacerbation of asthma. No anaphylactic reaction or multiple-organ life-threatening events occurred.

Discussion

This study indicates that 18 months' treatment with HDM SLIT in children with mild-moderate asthma led to inconclusive results about the clinical efficacy of the treatment. Changes in diurnal and nocturnal asthma scores, the primary outcome, were similar in the two treatment groups. Both groups achieved a similar reduction in the use of inhaled corticosteroids without compromising asthma control. Other secondary endpoints, such as lung function parameters and rhinitis score, did not show significant differences between the groups. One domain (severity) of QoL was improved in a sub-group of children (6–12 yr old) treated with SLIT.

The use of SIT in the treatment of dust mite allergy is usually assessed in clinical trials of between 12- and 24-month duration. In this study, the treatment duration of 18 months takes into account the ethical difficulties of enrolling children in a long-term, placebo-controlled study. Patient's inclusion at baseline occurred between September and November 2000, which is the optimal time of year to enroll symptomatic dust mite-sensitized patients due to the well-known significant increase in the mite allergen content of house dust during this season. Our outcomes included assessments 1 yr later (12 months after randomization), at the time corresponding to the 'peak' dust mite season, and during spring at the end of the study. We acknowledge that the dust mite load may be lower in spring than in autumn, which may have biased the outcomes in this study towards a lack of efficacy for the study treatment. Nevertheless, in our study, this bias seems unlikely because our data showed no significant changes in the level of dust mite allergens in bedding both at 12 months and at the end of the study.

Our results are not consistent with those of other controlled studies including mite-sensitized asthmatic children, which have shown that SLIT reduces symptoms (15, 18–20) and rescue medication use (15, 18) or improves respiratory function (17), when compared with placebo. In those studies, however, the pharmacological treatment of asthma (e.g. daily inhaled corticosteroids intake) was not considered to be a critical inclusion criteria, and there was a lack of

a clear step-down strategy for asthma pharmacotherapy.

We must consider four possible explanations for our failure to demonstrate the efficacy of immunotherapy.

First, there was the difficulty in enrolling patients who fulfilled all the inclusion criteria and, rather than extend our enrolment period indefinitely, we included fewer patients than planned. Therefore, our study was underpowered.

Secondly, the majority of patients in either treatment group had very mild asthma. Two-thirds of patients had mild asthma with low asthma symptom scores, and an average FEV₁ of 90% of predicted at baseline. In addition, all patients received with optimal pharmacologic treatment according to international guidelines (2). These data are consistent with those reported by Adkinson et al. (29) and recently by Maestrelli et al. (30) with subcutaneous SIT, which for no benefit or marginal but statistically significant benefit with SIT. Our study protocol indicates that investigators had to follow a gradual step-down approach for reduction in inhaled corticosteroids if the clinical symptoms and PEF variability were in an acceptable range. These instructions were correctly followed by the majority of the investigators, thus by the end of the study, both groups had achieved a more than 50% reduction in the use of inhaled corticosteroids. If we had aimed for a more significant reduction of inhaled corticosteroids this would probably have resulted in a difference in symptoms between the SLIT and placebo groups, but such a reduction in medication was unfeasible for ethical reasons. One also has to consider also the significant placebo 'management effect' observed in our study, which is the consequence of regular follow up, children and parent education, and encouraging self-management with diary cards.

A third possible explanation is that the dose of allergen administered was insufficient. However, this seems unlikely because our study was based on a high-dose SLIT protocol (350 times the subcutaneous immunotherapy dose), which follows international recommendations (10). The correlation between allergen dose and SLIT efficacy has not been extensively studied although, in a SLIT study using ragweed allergen extract from the same manufacturer, André et al. (31) showed a significant improvement of rhinoconjunctivitis in patients treated with high-dose 300 IR compared with patients treated with a lower dose (< 300 IR).

Our final reason is related to the efficacy of HDM-avoidance measures. At the entry in the

baseline, the mean levels of the Der p 1 measured in the mattresses of all patients (< 4 µg/g dust), was lower than the concentration of 10 µg/g needed to trigger the respiratory symptoms (1). In addition, the dust mite-avoidance measures applied in our study decreased the levels of Der p 1 antigens in the mattresses in both groups, thus probably reducing symptoms. Recently, Tonnel et al. (32) showed that among 120 patients with dust mite allergic rhinitis enrolled in a SLIT study, the use of antimite covers over a 2-month run-in period significantly improved the symptoms in 75% of patients. These results concur with those reported by Morgan et al. (33) but are in contradiction with those of Luczynska et al. (34) who did not find any improvement of asthma symptoms after the use of allergen-impermeable bedding.

Our analysis of the secondary *in vivo* and *in vitro* endpoint showed that there was a significant effect with SLIT. Immediate skin test response to dust mite allergen decreased significantly after 18 months of SLIT administration. A significant reduction in HDM skin sensitivity has previously been reported following SLIT in a number of studies (18, 32) but not in others (15–17, 19). Therefore, with sublingual and with subcutaneous SIT, a correlation between changes in skin reactivity and clinical symptoms is not always found.

The increase in IgE levels observed in the group treated with SLIT in our study agrees with reports from other SLIT studies (15–20). SIT is frequently associated with an increase in allergen-specific IgG₄ antibodies that is not always correlated with an improvement in clinical symptoms (22). In our study, a significant increase in *D. pteronyssinus* and *D. farinae*-specific IgG₄ was found in SLIT-treated group in comparison to the placebo group, indicating a positive immune system stimulation by SLIT. Other SLIT studies were contradictory, Bousquet et al. (17) found similar results to our study but others reported no change in IgG₄ levels (15, 16, 18, 20, 35). Although the rise in allergen-specific IgG₄ antibodies is a hallmark of subcutaneous SIT, the discrepancy in results observed with SLIT suggests that the peripheral immunologic mechanisms underlying SLIT differ from those underlying subcutaneous SIT. The putative role of the oral mucosa in the development of immune tolerance needs further investigation (22, 36, 37).

The safety of the SLIT high-dose regimen using the allergen of the same manufacturer was previously assessed in a dose-ranging study (38) and showed a good safety profile. In our study,

SLIT was well tolerated by children and mild-moderate local adverse events (oral/gastro-intestinal complaints) constituted the most frequent adverse events. Thus confirming again data reported by others (39, 40).

In addition to the good safety, one of the features of our study is the good compliance profile. Patients in our study had a low rate of dropout and temporary interruption of treatment. This was mainly due to the regular patient follow up during the study, but may also have been due to the use of sublingual tablets rather than sublingual drops. In the majority of SLIT studies, allergen extracts were administered by drops that must be kept under the tongue for 2 min before being swallowed. Such a procedure is not always easy, particularly for children, and when the volume increases to the maintenance maximal dose of 1 ml. Therefore, a tablet that allows gradual sublingual dissolution significantly improves the ease of use, patient's acceptability and, consequently, their adherence to treatment. In a previous study, where patients started SLIT with tablets then switched to the drops, patient's preference was significantly in favour of the tablets (38). Although it can be argued that the good adherence observed in the present study is due only to the specific conditions of a randomized clinical trial, in a recent open, 'real-life' SLIT study. Marogna et al. (41) reported a good adherence rate in 72% of the 511 patients studied.

In conclusion, our study in children with HDM-induced asthma treated for 18 months with SLIT showed that SLIT is well accepted, safe, and immunologically active but cannot provide significant additional immediate benefits when these patients are well managed with optimal antiasthma drug therapy in association with careful dust mite-avoidance measures. However, our results must be viewed in context whereby allergen SIT is known to be disease modifying and capable of inducing a reduction of the risk of asthma onset in patients with allergic rhinitis (42, 43) and, on the other hand, long-term inhaled corticosteroid therapy in children does not have a disease-modifying effect (44). Thus, children with early onset of allergic asthma and who are not treated with inhaled steroid therapy could be potential candidates for SLIT. Further studies are needed to define more precisely for which subgroups of asthmatic children.

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