

Original article

Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy

Background: The efficacy and safety of sublingual immunotherapy (SLIT) in patients with chronic rhinitis related to sensitization to house dust mites are still controversial.

Methods: After application of an anti-mite mattress cover, patients were only included in the study when the cumulative symptom score over a fortnight was greater than 70 out of a possible total of 168. Thirty-two of the 120 patients selected were randomized to receive SLIT for 2 years: 17 received placebo and 15 received the *Dermatophagoides pteronyssinus* and *D. farinae* 50/50 allergen extract.

Results: Significant between-group differences were observed after 1 year and persisted at the end of the second year for the rhinitis total score ($P < 0.02$), blocked nose score ($P < 0.01$) and nasal itching score ($P < 0.01$). Skin reactivity to house dust mites was significantly reduced in the group receiving house dust mite extract ($P < 0.03$). No statistical difference was observed between the two groups for medication scores, but a low medication consumption was observed in all patients. No serious and no systemic adverse reactions were reported.

Conclusion: This study indicates the superiority of active treatment vs. placebo, evaluated on efficacy criteria (rhinitis score) or objective criteria (skin reactivity). The availability of a solid form (tablet) could represent a progress in terms of patient acceptability.

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Allergen avoidance and specific immunotherapy are the only two available etiologic treatments for respiratory allergies. Subcutaneous immunotherapy has been validated for the treatment of asthma (1) and rhinitis (2). Brief episodes of pollen allergy constitute the best indication for this treatment modality, but it has been more difficult to establish its efficacy in perennial allergies, including house dust mite allergy (3, 4). Similar problems have been observed with sublingual immunotherapy (SLIT): it has been validated with pollen extracts, including in pediatric indications (5), but has been less extensively studied in house dust mite allergy. Contradictory results have been reported for SLIT in this indication: negative results for some studies (6, 7) and positive results for others (8–11). Some of these failures were probably due to the impact of mite avoidance in the placebo group. The recent Cochrane meta-analysis based on 22 placebo-controlled trials of SLIT in a total of 979 patients with rhinitis concluded on a significant reduction in both symptoms and medication requirements following immunotherapy with allergens in general. House dust mite studies comprised the majority of the perennial allergen subgroup, but fell short of statistical significance for both symptom and

medication scores (12). The study reported here presents two unusual features: the use of a tablet form, but especially a methodology complying with the usual rules of Good Medical Practice, i.e. application of optimal measures of house dust mite avoidance and exposure control (13, 14) by using an anti-mite mattress cover (15, 16) for each patient eligible for inclusion in the study.

Materials and methods

Patients

One hundred and twenty adult and pediatric patients, between the ages of 7 and 45 years, presenting with rhinitis with or without moderate asthma (GINA 2) and sensitized to house dust mites were pre-included in this study.

The pre-inclusion assessment comprised clinical history, skin prick tests and specific IgE assays (*Dermatophagoides pteronyssinus* and/or *D. farinae*). To be eligible for inclusion, the patient's clinical history had to clearly indicate the responsibility of house dust mites for the patient's symptoms. Skin prick tests to *D. pteronyssinus* and/or *D. farinae* (Stallergènes S.A., Antony, France) and specific IgE (CAP Pharmacia, Uppsala, Sweden) to *D. pteronyssinus* and *D. farinae* were performed on inclusion: mean wheal diameter ≥ 4 mm and

Table 1. Demographic characteristics and medical history of the patients randomized in the study ($n = 32$)

Characteristics	Active treatment ($n = 15$)	Placebo ($n = 17$)
Gender		
Male	8 (53%)	10 (58.8%)
Female	7 (47%)	7 (41.2%)
Age (years), mean $\pm$ SD (range)	23.8 $\pm$ 8.6 (12–38)	20.9 $\pm$ 8.1 (9–35)
Rhinitis		
Duration (years), mean $\pm$ SD (range)	10.4 $\pm$ 10.7 (1.3–35.2)	8.3 $\pm$ 7.0 (0.9–24.3)
Frequency		
Daily	12 (80%)	13 (76.5%)
Weekly	3 (20%)	4 (23.5%)
Prior desensitization treatment	5 (33%)	4 (23.5%)

radioallergosorbent test (RAST) $\geq$ class 2. A house dust mite nasal provocation test was also performed: a score on this test, three times higher than that of the control test, was considered to be positive.

Mite exposure was systematically investigated and measured for each patient and avoidance measures were completed by application of an anti-mite mattress cover. Daily clinical symptom and medication scores were collected for each patient for a period of 6 weeks after application of the mattress cover, and the last 2 weeks were used to establish a residual clinical score necessary for inclusion of the patients. Symptoms were scored according to a 4-point scale for each of the rhinitis criteria (blocked nose, rhinorrhea, sneezing, itching). This means a maximal score of 12 per day and 168 for 14 days (0: no symptoms; 1: symptoms present but not bothersome; 2: symptoms present and bothersome; 3: severe symptoms).

To be eligible for inclusion, patients had to have a rhinitis score equal to or greater than 70 despite application of the mattress cover: these very rigorous inclusion conditions led to the exclusion of a large number of pre-included patients: only 32 patients had a clinical score $\geq$ 70 during the 2 weeks preceding inclusion.

Patients or their parents gave their written consent to participate in this study, which was approved by the Lille Ethics Committee.

The main demographic characteristics and medical history of the randomized patients are summarized in Table 1. No significant difference was observed between the two treatment groups for these items.

Allergen preparation

A standardized *D. pteronyssinus* and *D. farinae* (50/50) mite extract was administered, initially in the form of sublingual drops during the dose progression phase, and then in the form of 100 index of reactivity (IR) tablets for the rest of the study (24 months).

The IR is a unit of allergenic activity specific to Stallergènes laboratory: a 100 IR extract is defined by its capacity to induce a mean wheal diameter of 7 mm in skin prick tests in a panel of 30 patients sensitized to the allergen considered.

Placebo drops and tablets had the same appearance and were supplied in the same packaging as the active substance.

Immunotherapy

The duration of treatment was 24 months, comprising a 2-week allergen extract dose progression phase with daily doses of 1, 3, 6, and 10 drops of the 1 IR/ml vial, followed by daily doses of 1, 3, 6, and 10 drops of the 10 IR/ml vial and finally 1, 2, 4, 8, 12, 16, and 20 drops of the 100 IR/ml vial.

Drops were deposited on a food support (lump of sugar or piece of bread) and had to be kept under the tongue for 2 min before being swallowed.

Maintenance treatment, lasting 23.5 months, consisted of one 100 IR tablet, taken each morning and kept under the tongue until complete dissolution.

The mean cumulative dose for the study population was about 47 500 IR, i.e. 1.28 mg of Der p 1 and 1.47 mg of Der f 1 (47 486 IR for the active treatment group and 47 355 IR for the placebo group) for the total duration of the study, i.e. 24 months.

Symptom and medication scores

Patients were asked to complete a self-assessment diary each day, scoring the symptoms of rhinitis (rhinorrhea, sneezing, nasal itching and blocked nose) in the same way as before pre-inclusion. Conjunctivitis and asthma were scored as being either present or absent.

The use of symptomatic medications was also recorded daily: number of cetirizine tablets used as required to treat moderate symptoms; number of puffs of nasal flunisonide, which was only allowed to be used for brief periods to treat persistent, moderately severe symptoms; dose of prednisolone, only to be used in the case of persistent, disabling symptoms, and number of puffs of salbutamol in patients presenting concomitant asthma symptoms.

Skin prick tests

Quantitative skin prick tests with Stallergènes standardized *D. pteronyssinus* and *D. farinae* extracts at dilutions of 6, 19, 56, 167 and 500 IR/ml were performed by the investigators, under blind conditions, before starting treatment and then after 1 and 2 years of treatment.

Nasal provocation test

The nasal provocation test was performed with *D. pteronyssinus* and *D. farinae* 50/50 allergen extract using increasing concentrations of 0.1–100 IR/ml at the dosage of one 100 μ l puff into each nostril. A score was established (0: absent, 1: partial or moderate, 2: severe) for each of the rhinitis symptoms (sneezing, rhinorrhea, blocked nose and nasal itching) and (1: present, 2: absent) for conjunctivitis.

A control test was first performed with the diluent and the nasal provocation test was considered to be positive when the score was three times greater than that obtained on the control test. The test was performed at the beginning the study and at the end of each year of treatment (17).

Laboratory parameters

Specific IgE and IgG₄ assays (Pharmacia, Sweden) for the two house dust mites, *D. pteronyssinus* and *D. farinae*, were performed on three occasions: on inclusion, at 1 year and at the end of 2 years of treatment. Serum samples were stored until the end of the study and were assayed in a single series in a centralized laboratory (Laboratoire Marcel Mérieux, Lyon, France). Specific IgE levels were expressed in kIU/l and IgG₄ levels were expressed as a percentage of the reference serum.

House dust mite avoidance and exposure rate

At the investigator's request, an environment consultant performed a home visit for each patient included in the study. This

consultant gave a demonstration of adequate cleaning of the patient's bedroom. This consultant also vacuum-cleaned the patient's bedroom (OPTIMA, Vorwerk, Marly le Roy, France) and assayed mite guanine in the fine dust collected (18) [Acarex-Test®, KARAPHARM, Marseille, France: semiquantitative determination with results expressed in four classes (0: less than 600 µg/g, 1: between 600 µg/g and 2500 µg/g, 2: between 2500 µg/g and 10 000 µg/g, 3: more than 10 000 µg/g of dust)].

An anti-mite mattress cover (Housse ACB, MEDECA AB, Uppsala, Sweden) was placed on each patient's bed. Determination of allergen levels was repeated at the end of the first and second years of treatment.

Statistical analysis

Qualitative data were analyzed by the chi-square test or Fisher's exact test. Symptoms, medication intake, skin tests and house dust mite-specific IgE and IgG4 were analyzed statistically by nonparametric tests. The Wilcoxon rank sum test was used for intragroup analysis and the Mann-Whitney *U*-test was used for intergroup analysis. All tests were two-tailed, and the level of significance was set at 0.05.

Results

Patients

Thirty-two patients were randomized: 15 in the active treatment group [A] and 17 in the placebo group [P]. The mean age was 23 ± 8.6 years (range: 12–38 years) for the active treatment group and 20.9 ± 8.1 years (range: 9–35 years) for the placebo group. On inclusion, the patients presented a mean symptom score of 100.09 (for a maximum score of 168), with no significant difference between the two groups.

Fourteen patients (five in the active treatment group and nine in the placebo group) discontinued treatment before the end of the second year, due to lack of efficacy in six cases (three in the active treatment group and three in the placebo group) and adverse events in two cases (one case of itching/burning of the mouth in the active treatment group and one case of respiratory tract infection in the placebo group).

The 32 patients included frequently presented a family history of rhinitis (75%); rhinitis had been present for an average of 9.3 ± 8.8 years and 78% of the patients included reported daily symptoms.

Twenty-seven patients had received symptomatic treatment for their allergic rhinitis during the 12 months preceding inclusion in the study.

Overall, the percentage of patients dropping out of the study was not significantly different ($P = 0.265$) between the active treatment group (33.3%) and the placebo group (52.9%). Figure 1 presents an outline of the study design.

Symptom scores

The symptom scores were reported as the daily median, and the first and third quartile for each month of

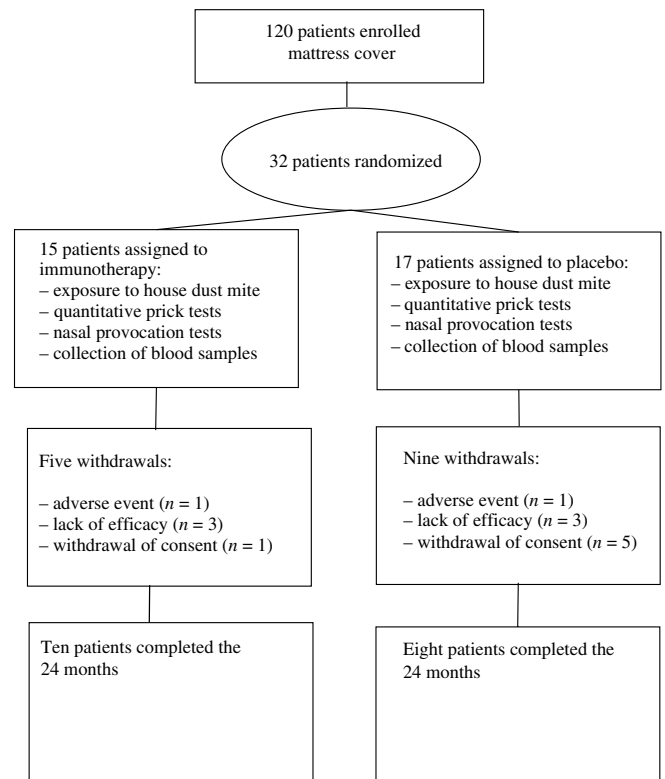


Figure 1. Study plan.

treatment. The total rhinitis score (Fig. 2) decreased regularly by the first month of treatment with a marked difference between the two groups by the sixth month and until the end of the study. The differences in area under the curve were statistically significant during years 1 ($P < 0.03$) and 2 ($P < 0.02$).

Rhinitis symptoms were significantly different during the first and second year of treatment in terms of nasal itching ($P = 0.01$) and blocked nose ($P = 0.01$).

Intra-group analysis performed on rhinitis symptom scores demonstrated improvement over time for all parameters: a significant improvement ($P < 0.01$) of rhinorrhea, itching, blocked nose and total rhinitis score was observed during the first year of treatment compared with baseline, while no improvement was observed in the placebo group (Table 2). During the second year of follow-up, a similar improvement was observed in the active treatment group, but some parameters also decreased in the placebo group (sneezing and total rhinitis score).

Symptomatic medication

Medication scores were not modified during the 24 months of treatment. No significant difference was observed between the two treatment groups, but medication consumption remained low in all patients (Fig. 3).

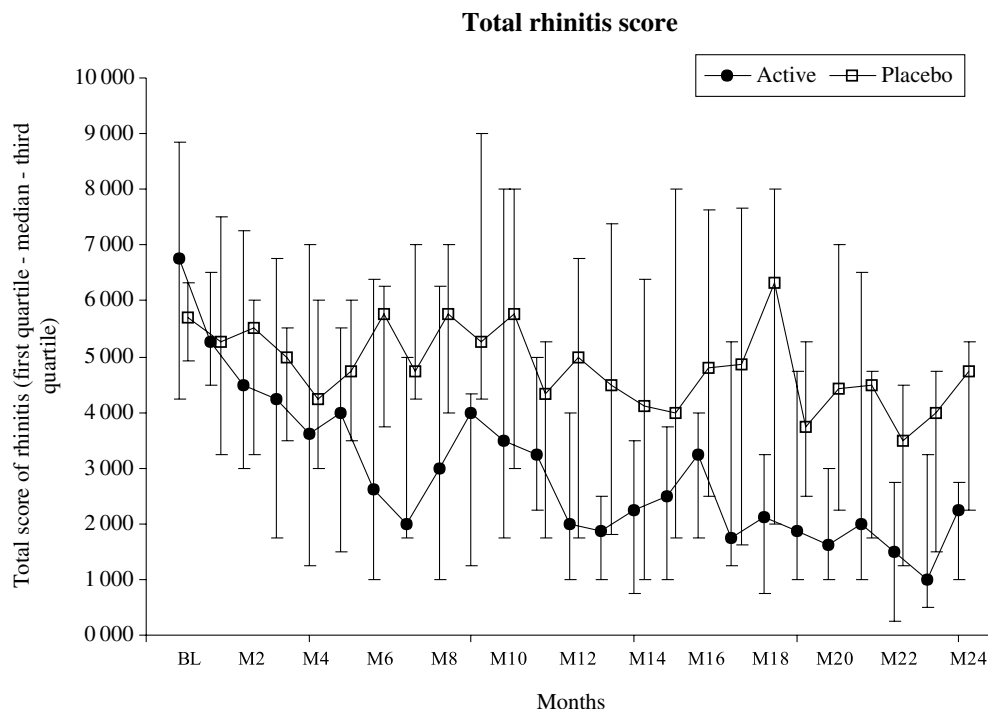


Figure 2. Total rhinitis score (first quartile, median, third quartile) in active treatment (●) and placebo (□) groups.

Table 2. Course of symptom scores during the study

Symptom	Group	YR1 – BL	P	YR2 – BL	P
Sneezing	Active treatment	-0.16 ± 0.41	0.71	-0.37 ± 0.43	0.92
	Placebo	-0.09 ± 0.62		-0.39 ± 0.6	
Rhinorrhea	Active treatment	-0.65 ± 0.73	0.12	-1.03 ± 0.48	0.11
	Placebo	-0.24 ± 0.72		-0.53 ± 0.83	
Nasal itching	Active treatment	-0.54 ± 0.56	0.01	-0.99 ± 0.77	0.01
	Placebo	$+0.02 \pm 0.56$		-0.18 ± 0.59	
Blocked nose	Active treatment	-0.97 ± 0.76	0.01	-1.47 ± 0.63	0.01
	Placebo	-0.28 ± 0.72		-0.59 ± 0.83	
Total rhinitis score	Active treatment	-2.33 ± 1.9	0.03	-3.86 ± 1.27	0.02
	Placebo	-0.58 ± 2.3		-1.69 ± 2.60	

YR1 – BL, year 1 minus base line; YR2 – BL, year 2 minus base line.

Skin prick tests

Skin prick tests to house dust mites were positive for all patients (mean wheal diameter for *D. pteronyssinus*: 7.5 ± 1.8 mm in the active treatment group vs. 9 ± 3.3 mm in the placebo group; mean wheal diameter for *D. farinae*: 7.7 ± 3.2 mm vs. 8.3 ± 2.3 mm). One patient had a positive test to cockroach and four patients had positive tests to cat fur, but with no clinical significance.

Skin reactivity measured by the quantitative skin prick test technique decreased significantly for *D. pteronyssinus* ($P = 0.038$) and *D. farinae* ($P = 0.007$) in the active treatment group compared with placebo between the beginning and the end of treatment. The variation of skin reactivity was not statistically significant after 1 year of treatment.

Exposure to house dust mites

On inclusion, before application of the anti-mite mattress cover, the median quantity of mite guanine in house dust was situated in classes 3 (between 2500 and 10 000 µg/g) and 4 (more than 10 000 µg/g), while, at the visit following application of the anti-mite mattress cover, the median quantity of mite guanine was situated in the 600–2500 µg/g range and subsequently rose after 1 year and 2 years of treatment (median value in the 2500–10 000 µg/g range), possibly reflecting less rigorous application of avoidance measures or a lower level of attention due to improvement of symptoms. All patients included remained exposed to a minimum level of house dust mites throughout the study (Table 3).

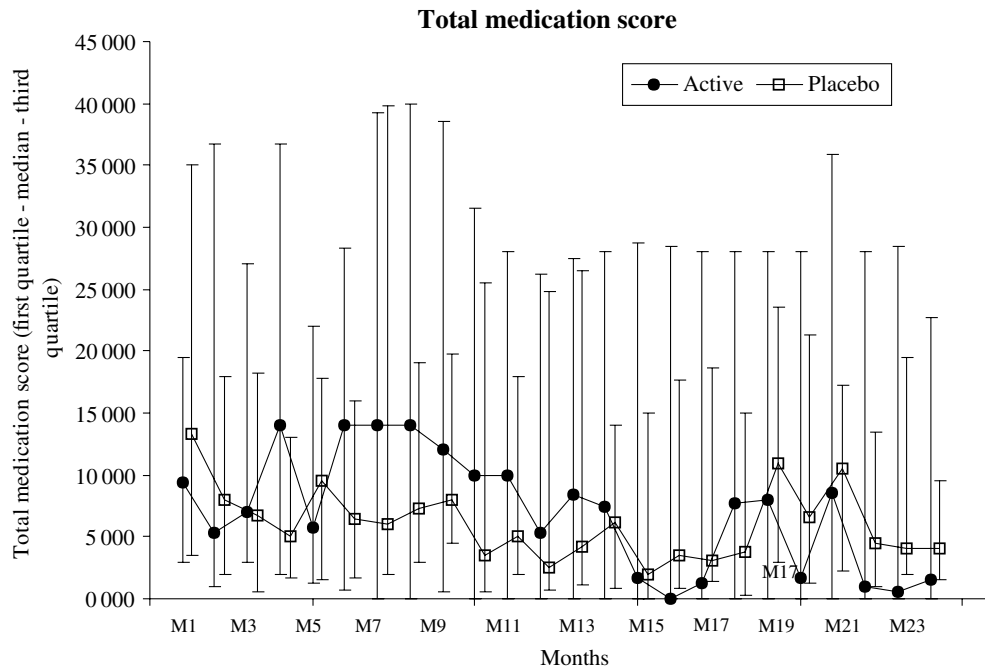


Figure 3. Total medication score (first quartile, median, third quartile) in active treatment (●) and placebo (□) groups.

Table 3. Change in exposure to house dust mite (mattress samples)

Acarex class (µg/g dust)	Before mattress cover		After mattress cover		After 1 year		After 2 years	
	Active treatment (n = 15)	Placebo (n = 17)	Active treatment (n = 15)	Placebo (n = 17)	Active treatment (n = 10)	Placebo (n = 13)	Active treatment (n = 10)	Placebo (n = 10)
Class 0 (<600)	0	0	5	6	0	1	0	3
Class 1 (600–2500)	3	4	10	6	2	4	5	2
Class 2 (2500–10 000)	5	4	0	5	8	7	4	5
Class 3 (>10 000)	7	9	0	0	0	1	1	0

Nasal provocation test

The median threshold dose was 0.1 IR before starting treatment and 1 IR after the first year of treatment in the active treatment and placebo groups (NS).

The median threshold dose at the end of treatment (year 2) was 10 IR for the active treatment group and 1 IR for the placebo group, but no significant difference was demonstrated between the two groups, probably due to the small number of patients tested (nine in the active treatment group and 10 in the placebo group).

Laboratory parameters

No significant difference was demonstrated between the two treatment groups for specific IgG₄ assays. However, a significant reduction of specific *D. pteronyssinus* IgE levels (mean: –22 kIU/l, SD = 34.8, from 139 to 117 kIU/l) was observed between the 12th month of treatment and the end of the study in the active treatment group, while

no significant difference was observed in the placebo group (mean: +3.9 kIU/l, SD = 30, from 57 to 61 kIU/l). The inter-group variation was significant with $P = 0.045$.

Safety

Three patients (one in the active treatment group and two in the placebo group) presented adverse events: itching of the lips and epigastric pain (active treatment group) and manifestations related to asthma (placebo group). No serious adverse effect was reported.

Discussion

This study evaluated the efficacy of SLIT in house dust mite-allergic rhinitis. This long-term, randomized, double-blind study compared treatment with an active allergen extract vs placebo. It comprised a preliminary allergen avoidance phase designed to more closely reproduce usual

management conditions of patients sensitized to house dust mites. This initial phase obviously induced inclusion difficulties: out of a sample size of 120 preselected patients, only 32 were able to be randomized, as eligible patients had to present a sufficiently high symptom score (symptom score equal to or greater than 70 out of a maximum of 168 during the fortnight preceding randomization) after application of the anti-mite mattress cover for 6 weeks.

Following validation of subcutaneous immunotherapy, an increasing number of studies have been published concerning the role and the efficacy of SLIT. Many of these studies have evaluated the place of SLIT in the treatment of pollen allergy (grass pollens, tree pollens, *Parietaria*, olive, etc.), but only very few studies have been devoted to perennial allergy, especially house dust mite allergy. A review of the literature reveals a number of negative studies. Hirsch et al. (6) conducted a study in 30 house dust mite-allergic children presenting with asthma and rhinitis; the study lasted 12 months, but used low doses (five times the dose generally used by subcutaneous injection) and failed to demonstrate any significant difference between the active treatment group and the placebo group. Another study, conducted by Guez et al. (7) in a group of 56 patients, also gave negative results, but demonstrated the excellent safety despite the high doses used. One of the studies reporting favorable results for SLIT is that conducted by Passalacqua et al. (8): 19 patients were treated for 2 years and obtained a reduction of the symptom score by the second semester of treatment. These patients also presented a reduction of the conjunctival provocation test associated with an original laboratory criterion, i.e. reduction of ICAM-1 expression on conjunctival epithelial cells. Bousquet et al. (9) studied patients sensitized to house dust mite (children and adults), predominantly suffering from asthma. High doses were used: 200 times the doses administered by subcutaneous injection. No significant difference was observed between the groups in terms of symptom scores or medication consumption, but lung function parameters, especially FEV₁, were significantly improved during the second year of treatment. More recently, Pajno et al. (10) also reported favorable results in 21 asthmatic children mono-sensitized to house dust and studied for 2 years: a reduction of both symptoms and medication score was observed during the second year.

Comparison of the two immunotherapy techniques, sublingual vs subcutaneous, has been the subject of two recent studies performed in 1999 by Mungan et al. (11) in patients sensitized to house dust mites and in 2002 by Kinchi et al. (19) with birch pollen extracts. Both studies used high doses of allergen (80–210 times the doses generally used by subcutaneous injection). They demonstrated the equivalent efficacy of the two modalities in terms of clinical symptoms and medication consumption, although the study by Mungan et al. demonstrated a more marked efficacy for SLIT on rhinitis symptoms than on asthma symptoms.

An important argument in favor of SLIT is the absence of adverse effects in these patients presenting with perennial

allergy, as, except for study by Tari et al. (20), performed in 1990, which reported major adverse effects (severe or moderate asthma attacks) despite low doses of SLIT (five times the doses administered by subcutaneous injection). All subsequent studies performed with mites or pollen allergen extracts emphasized the safety of SLIT (21, 22), with only a few cases of itching lips or tongue or mild dyspeptic disorders, as observed in our study.

Another point that has been controversial for a long time is the long-term efficacy of the SLIT. A recent study published by Di Rienzo et al. (23) reported the long-term efficacy of SLIT in asthmatic children sensitized to house dust mites. This study compared 60 children divided into two matched groups: 35 received SLIT for 4–5 years, while 25 only received drug treatment. Analysis of the results showed a significant difference for both the symptom score ($P < 0.001$) and the consumption of symptomatic medications ($P < 0.01$). An improvement of peak flow was also observed. This improvement was maintained 4–5 years after stopping immunotherapy. However, in contrast with subcutaneous immunotherapy (24, 25), SLIT (23) does not appear to decrease the risk of appearance of new sensitizations in children treated with this modality, but this might be due to the low doses used by Di Rienzo et al. (23).

Conclusion

This study confirms the efficacy of SLIT in house dust mite allergy. This improvement was obtained by using high doses and mainly concerned the rhinitis symptom scores, while medication consumption remained unchanged. Other interesting points concern the reduction of cutaneous reactivity to the allergen and reduction of the nasal provocation test to house dust mites. No significant adverse effects were observed despite the considerable doses of allergen ($\times 200$ the dose administered by subcutaneous injection). This study also raises the problem of the route of administration during maintenance treatment: in this study, patients were treated with sublingual dissolving tablets, which probably facilitate the conditions of administration of the medication and consequently the compliance with treatment. Extension of this mode of administration certainly deserves further investigation.

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