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Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study

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Summary

Background Subcutaneous immunotherapy for respiratory allergy has shown a long-lasting efficacy after its discontinuation, whereas this evidence is still lacking for sublingual immunotherapy, despite the fact that it is widely used.

Objective We aimed to evaluate whether a long-lasting effect of SLIT occurs, in a prospective parallel group controlled study.

Methods Sixty children (mean age 8.5 years) suffering from allergic asthma/rhinitis due to mites were subdivided into two matched groups: 35 underwent a 4- to 5-year course of SLIT with standardized extract and 25 received only drug therapy. The patients were evaluated at three time points (baseline, end of SLIT and 4 to 5 years after SLIT discontinuation) regarding presence of asthma, use of anti-asthma drugs, skin prick tests and specific IgE.

Results We found that in the SLIT group there was a significant difference vs. baseline for the presence of asthma ($P \leq 0.001$) and the use of asthma medications ($P \leq 0.01$), whereas no difference was observed in the control group. The mean peak expiratory flow result was significantly higher in the active group than in the control group after 10 years. No change was seen as far as new sensitizations were concerned. Specific IgE showed a near-significant increase (baseline vs. 10 years, $P = 0.06$) only in the control group.

Conclusion Our study demonstrates that sublingual immunotherapy is effective in children and that it maintains the clinical efficacy for 4 to 5 years after discontinuation.

Keywords asthma, children, long-lasting effect, respiratory allergy, rhinitis, sublingual immunotherapy

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Introduction

Allergen-specific immunotherapy (IT) is widely used in the treatment of respiratory allergy and it is presently recognized as a biological response modifier as it is capable of affecting at the earliest stages the immune response to the offending allergen. In fact, the term 'allergen vaccination' has been proposed for this practice [1]. The mode of action of IT is complex, but recent experimental data suggest that IT redirects the lymphocyte response towards the Th1-type and reduces the production of cytokines, such as IL-4, IL-5 and IL-13 [2–5]. These mechanisms of action make IT unique, and different from any other pharmacological treatment. First, at variance with drugs, IT is capable of modifying the natural history of allergic disease. This fact was demonstrated in a clinical paediatric study as early as 1968 [6]. The mentioned study raised some criticisms because of its methodological limits, but the observation was then confirmed in more rigorous trials, such as the PAT study [7]. Secondly, IT is capable of preventing the onset of new sensitizations, as clearly demonstrated in children and adults in several studies [8–10]. Finally, IT maintains its clinical efficacy even for 3 to 5 years after its discontinuation, as confirmed by several studies conducted with different evaluation criteria [11–13]. The aforementioned characteristics (long-lasting effect, preventive effect) have been demonstrated only for the subcutaneous route of IT (SCIT).

Sublingual IT (SLIT) is presently widely used, especially in European countries; it has the main aim of reducing the risks of severe adverse events, and of making the treatment more acceptable to the patient. The short-term clinical efficacy of SLIT has been repeatedly demonstrated and confirmed in pollen-induced allergy, in patients with either rhinitis or asthma (for review see [14]). Concerning respiratory allergy due to mites, there are seven controlled studies [15–21]; four out of them were performed in children [15, 16, 19, 21] and only one reported unsatisfactory results [16], but no data are available on the long-term outcome. On the other hand, SLIT showed an excellent safety profile in both adults and children, as testified by the controlled trials [22] and the post-marketing surveillance studies [23, 24]. Noteworthy is that no severe systemic side-effect has ever been reported in more than 15 years. It is conceivable that

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the mode of action of SLIT does not differ greatly from that of subcutaneous IT, and that also SLIT is capable of modifying the natural history of the disease, but so far there is no datum concerning the duration of its effect after discontinuation. The possibility of achieving a long-lasting efficacy, in addition to the favourable risk : benefit ratio, would further justify the use of SLIT, especially in children.

We report here the results of a 10-year prospective, open, controlled study assessing the long-lasting efficacy of SLIT in paediatric patients with mite allergy.

Table 1. Baseline characteristics

	SLIT group	Control group	Comparison
Patients	35	25	
Mean age	8	9	*t*-test $P = NS$
Age range	3–17	4–17	
M/F	18/17	13/12	χ^2 $P = NS$
Single sensitization	16 (46%)	16 (60%)	χ^2 $P = NS$
Rhinitis alone	4 (11.4%)	2 (8%)	χ^2 $P = NS$
Asthma + rhinitis	31 (88.6%)	23 (92%)	χ^2 $P = NS$

Methods

Overall description

The study is a prospective, open, parallel-group controlled trial. Among 60 children, seen at our department between 1989 and 1990, 35 received SLIT for 4 to 5 years and 25 served as control group, with drug therapy only. Clinical evaluation (including peak expiratory flow measurement when possible) was performed regularly at 6-month intervals, whereas skin prick tests and IgE measurement were performed at baseline, at the end of the SLIT course and 4 to 5 years after discontinuation.

Patients and diagnosis

Sixty children (51.7% male, mean age 8.3 years, age range 3 to 17), seen at our department in 1990 were diagnosed as having allergic rhinitis and/or mild to moderate asthma due to house dust mites. The diagnosis was based on clinical history (perennial or near-perennial symptoms), clinical evaluation, skin prick test (> 3 mm) and RAST assay (at least class III) positivity. In particular, the presence of one or more asthma symptoms (wheezing, chest tightness and cough in the absence of respiratory infections) and their frequency in the past 3 months was assessed at baseline and subsequent visits. When asthma was not overt, a pulmonary function test with methacholine challenge was also performed when possible (practically, only in children aged 6 to 7 or more). Among the children, 28 were sensitized to mites alone, whereas the remaining had concomitant sensitizations to grasses and parietaria, but in all cases mites were responsible for perennial symptoms. The patients were therefore eligible for IT administration, according to international guidelines [1]. After detailed information about the modality and goals of SLIT, the parents of 35 patients agreed to begin the treatment, whereas 25 preferred to continue with pharmacological treatment only. The demographic characteristics of the two groups are shown in Table 1.

SLIT and concomitant treatments

The prescribed SLIT (ALK-Abellò, Milan, Italy) was an extract of *Dermatophagoides pteronyssinus* and *D. farinae* in equal proportion prepared as aqueous drops, to be taken in the morning, the patient being fasted. The induction phase, with gradually increasing amounts until reaching the maintenance dose, lasted 30 days. Subsequently, the maintenance dose of seven drops (corresponding to 1.12 μg of group 1 mite allergen and 0.56 μg of group 2 allergen) had to be taken twice weekly. The SLIT was administered continuously during the whole year and its duration was 4 to 5 years, as suggested in the current guidelines. The extract was standardized according to an in-house reference, so that the cumulative dose given per year was 116.5 μg group 1 and 58.2 μg group 2 allergens.

All patients, irrespective of SLIT, were prescribed an appropriate pharmacological treatment to be used as needed or regularly according to symptoms, as follows: cetirizine or loratadine (10 mg once daily), inhaled beclometasone (200 to 800 μg/day), inhaled salbutamol (one to four puffs, 100 μg per puff). Short courses of oral betametasone (1.5 to 4 mg/day) were allowed in the case of exacerbation of asthma and/or rhinitis. Moreover, allergen avoidance measures were always recommended, including: mattress and pillow impermeable covers; careful and frequent vacuum cleaning; and removal of carpets, curtains and pets from the bedroom.

Evaluated parameters

All patients were followed-up in regular clinical visits at 6- to 8-month intervals, as routinely performed in all outpatients. At each visit, the presence and the frequency of asthma symptoms were recorded. This allowed grading the severity of asthma as intermittent, mild, moderate and severe, according to the Global Initiative for Asthma (GINA) criteria [25]. Also, the use of anti-asthma therapy (inhaled corticosteroids and/or bronchodilators) in the previous 3 months was assessed at each visit. The drug treatment was modified case by case, based on the severity and frequency of symptoms. All patients were instructed to measure their peak expiratory flow rate (PEFR) twice daily, as suggested by guidelines. In particular, they were recommended to carefully register it in the month preceding each visit, in order to use the mean of the morning measurements as an evaluation parameter.

Skin prick tests and RAST assay (CAP System, Pharmacia, Sweden) were performed at baseline, in correspondence of the end of SLIT course and 4 to 5 years later (9 to 10 years after baseline assessment). Skin tests were carried out with a panel of biologically standardized allergens (ALK-Abellò, Milan, Italy), including: mite, grasses, *parietaria*, olive, birch, cat and dog dander, *alternaria* and *aspergyllus*.

Statistical analysis

The analysis for presence/absence of asthma was performed with the chi-square test, whereas the use of anti-asthma medications and change in IgE class was analysed by means of non-parametric tests (Wilcoxon sum rank test for intragroup analysis and Mann–Whitney *U*-test for intergroup analysis). Differences in children's age at baseline and changes in PEFR were analysed by means of parametric test (ANOVA). Values of P lower than 0.05 were considered statistically significant. All

statistical analysis was done by means of a standard statistical software (BMDP Inc., Los Angeles, CA, USA).

Results

The two groups of paediatric patients did not differ concerning the baseline demographic and clinical characteristics, as shown in Table 1.

Figure 1 summarizes the clinical results. At the end of SLIT treatment and 4 to 5 years after SLIT discontinuation, there was a significant reduction in the presence of asthma in the treated patients, as compared with baseline ($P \leq 0.001$, chi-square test). On the other hand, in the control group no clinical change could be observed after 5 and 10 years of follow-up. Also, there was a highly significant difference between the two groups, at both the end of SLIT and 5 years later ($P \leq 0.001$, chi-square test). In parallel, concerning the use of anti-asthma medications (during the previous 3 months), we could observe a significant difference between the two groups as well (Table 2). These differences were also statistically significant at the end of the SLIT course. Concerning the PEFR measurement, at the end of the trial we had available the data at all the three time points for 22/35 patients of the SLIT group and 16/25 patients of the control group, who registered their morning PEFR at least in the week preceding the visit. The PEFR missing data are essentially due to non-compliance or to the fact that at the beginning of the study, some patients were too young to perform the measures. The mean values of PEFR at the three time points are shown in Fig. 2. There was an expected increase of the PEFR over the time, due to the growth, but a significant difference between the two groups was apparent 10 years after the beginning of the study. Concerning the onset of new sensitizations, as shown in Table 2, there was no significant difference between the two groups. Only three patients in the SLIT group and two patients in the control group with single sensitization at baseline, developed new skin positivities during 10 years. The IgE class remained unchanged in the SLIT group throughout the observation period, whereas an increase near to statistical significance ($P = 0.06$, data not shown) could be detected in the control group when comparing the baseline value with the value obtained 9 to 10 years later.

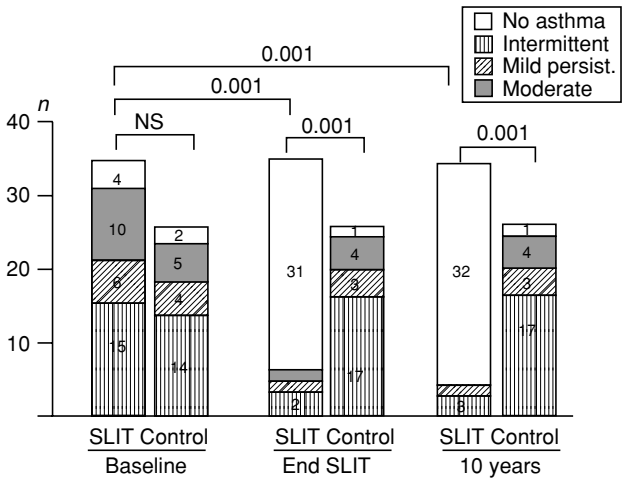

Fig. 1. Number of patients with different asthma severity, or without asthma, at the three time points. Significant intragroup and intergroup *P*-values are indicated upon the bars.

Table 2. Use of anti-asthma drugs and multiple sensitizations: evolution over the follow-up time period

	Baseline	End SLIT	10 years	*P*
Number of patients taking anti-asthma medications				
SLIT	31/35	4/35	3/35	0.001
Controls	23/25	24/25	24/25	NS
P	NS	0.001	0.001	
Number of patients with multiple sensitizations				
SLIT	19/35	21/35	22/35	NS
Controls	9/25	11/25	11/25	NS
P		NS	NS	NS

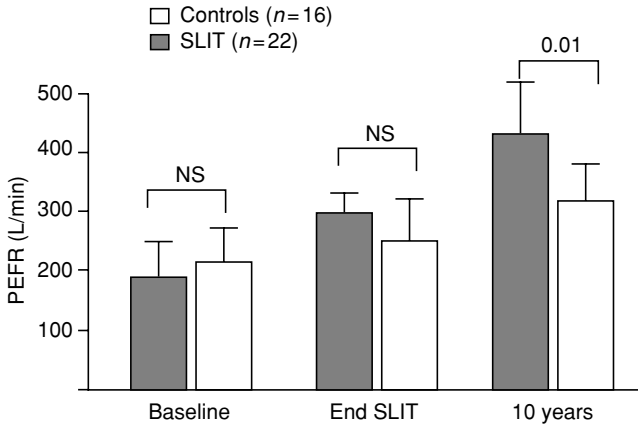

Fig. 2. Mean PEFR (L/min) ± SEM in the two groups of patients at the three time points. Inter-group *P*-values are indicated upon the bars.

Discussion

SLIT is now accepted as a valuable alternative to subcutaneous IT for the treatment of respiratory allergy in both adults and children [14]. Nevertheless, one of the major concerns with SLIT is that there is no experimental evidence of its preventive or long-lasting efficacy, at variance with SCIT [26]. Indeed, SLIT is a matter of the last 10 years and since its introduction the major goal of the clinical trials was to assess the clinical efficacy and the safety of the treatment. Therefore it is not surprising that, for instance, pharmacosurveillance studies have been published only during the last 3 years, and that long-term evaluations are still lacking. We provide herein, for the first time, data from a 10-year follow-up concerning the capacity of SLIT to modify the natural history of the allergic disease and to maintain a long-lasting effect in a paediatric population.

The study is open, but it is not feasible for both ethical and practical reasons to perform such a long follow-up in a blinded fashion. The ethical committee, in fact, asked that parents had to choose the treatment regimen (either SLIT or drug therapy) for their children. On the other hand, all the studies investigating the long-lasting effects of immunotherapy were

open-controlled, except for the trial by Walker and colleagues [13]. Indeed, the principal aim of our study was to evaluate whether SLIT is capable of maintaining its clinical effect for years after discontinuation, whereas the clinical efficacy *per se* was assumed as sufficiently demonstrated. To do that, over a 10-year period, we based our observations mainly on clinical evaluation, which was the only parameter applicable to all children at baseline. In a certain sense, our results repeat those obtained by Johnstone [6] with subcutaneous IT, but in our case the patients were carefully selected, immunotherapy was performed only for one allergen (dust mites) and a standardized extract was used. Moreover, the present data come from a 'real' everyday situation; thus, no bias due to the experimental conditions should be expected.

There is increasing evidence that SLIT is effective on both rhinitis and asthma [18, 27], and that it exerts some immunological effects in the target organs of the allergic inflammation [17, 28, 29]. Moreover, it has been shown that SLIT modulates the allergen-specific T lymphocyte response *in vitro* [30] and increases the IgG4 : IgE ratio *in vivo* [31]. Therefore, we can suppose that SLIT exerts, similarly to injection IT, a systemic action and is capable of modulating the specific immune response to allergens. Based on these considerations, it is reasonable to expect that also SLIT can maintain a long-lasting efficacy once discontinued. The results of our clinical study confirm the hypothesis and suggest that 4 to 5 years of continuous treatment represent an optimal SLIT duration in mite allergy. It remains to be demonstrated whether also shorter treatments (e.g. 1 or 2 years) can have a long-lasting effect. Despite the apparent long-lasting action, no appreciable effect could be seen on the onset of new sensitizations, in contrast to what was observed in previous studies [8–10] with injection IT.

The long-lasting effect is of particular relevance in paediatric patients, where a preventive effect on asthma onset and a prolonged duration of this effect are expected. SLIT seems to meet this expectation, in association with an optimal safety profile.

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