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Original article

Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites

Background: The clinical efficacy of sublingual immunotherapy (SLIT) in mite allergy and in mild disease is still a matter of debate, thus we performed a long-term clinical trial.
Methods: The study was randomized, double-blind and placebo-controlled. After a 1-year assessment, 68 patients with mild rhinitis with/without asthma due to mites were randomized to drugs + placebo or drugs + SLIT for 2 years. Sublingual immunotherapy was given as soluble tablets of monomeric carbamylated allergoid. Clinical scores for asthma and rhinitis (0, absent to 3, severe) and drug consumption were assessed by diary card in the period November–February. Quality of life was assessed before and after each observation period and pharmaco-economy data were evaluated as well.
Results: Fifty-six patients completed the study. The rate of dropouts was similar in the two groups. No relevant side effect was reported. There was a significant reduction of total clinical scores ($P < 0.05$) in the active group *vs* placebo at the first year, but not at the second whereas nasal obstruction significantly improved in both years ($P < 0.05$). The reduction of drug intake score was significant only at the first year. No change was observed concerning most of the Short Form-36 items, because at baseline all patients displayed a normal profile. A significant change in SLIT group was seen for the item 'change in health status'. The need for extra visits was significantly lower in the active group (25% *vs* 43%).
Conclusions: Sublingual immunotherapy was clinically effective and safe in mite-induced mild disease.

G. Passalacqua[1], M. Pasquali[1], R. Ariano[2], C. Lombardi[3], A. Giardini[4], I. Baiardini[1], G. Majani[4], P. Falagiani[5], M. Bruno[5], G. W. Canonica[1]

[1]Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa; [2]Allergy Unit, Bordighera Hospital, Imperia; [3]Allergy Service, Department of Internal Medicine, S. Orsola Hospital FBF, Brescia; [4]Psychology Unit, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Montescano (PV), Italy; [5]Lofarma S.p.A., Milan, Italy

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Giovanni Passalacqua, MD
Allergy and Respiratory Diseases
Department of Internal Medicine
Padiglione Maragliano
L.go R. Benzi 10
16132 Genoa
Italy

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Allergen-specific immunotherapy (IT) is a cornerstone in the management of respiratory allergy (1), and its clinical value is nowadays well recognized. In general, the clinical efficacy (reduction of symptoms and need for medications) of IT seems to be greater in pollen than in mite-induced allergy (1–4). This is probably due to the fact that in the case of dust mite allergy the continuous, although variable, exposure to an allergen sustains a chronic inflammation where the role of immunoglobulin E (IgE) and mast cells is less relevant than in pollinosis.

Starting from the earliest attempts, IT has been administered subcutaneously but due to safety aspects (5, 6) in the last 20 years new routes of administration have been investigated (7) and developed. Among these, the sublingual route (sublingual immunotherapy, SLIT) appeared to be the most promising alternative to the traditional IT. In 1998, the World Health Organization based on an extensive review of the literature, concluded that SLIT was a viable alternative to the injection route (1). These conclusions were subsequently confirmed in the recent ARIA (allergic rhintis and its impact on asthma) guidelines that extended the indication of SLIT to children also (8). Also in the case of SLIT, the effects in mite respiratory allergy were quantitatively less relevant than in pollen allergy, and statistically significant results were often obtained only with long-term treatments (9–11). Moreover, in children, SLIT proved effective only in those subjects with more severe rhinitis symptoms (12). Therefore, there are still some concerns about the indications and efficacy of SLIT in mild disease.

To date, it is recognized that the simple measurement of objective parameters or symptomatic changes does not provide a full evaluation of the effects of a given treatment, but the patients' perception also plays a relevant role. This is the reason why the assessment of quality of life (QoL) is assuming a more and more

important role in clinical trials, especially in allergy (13, 14). In association with the patients' perception of the impact of disease on his/her life, there is an another parameter that can provide further information about the subject's well-being: the so-called 'satisfaction' that is the cognitive product of the comparison between expectations and reality (15, 16). In the case of IT in general, and SLIT in particular, there are few data concerning the QoL aspects (11). Aim of the present study was to evaluate the clinical efficacy and the safety of SLIT over a 2-year period in patients suffering from mild rhinitis due to dust mites. The effects on QoL were assessed as well.

Methods

Study design

This was a multicentre, randomized, placebo-controlled, two parallel-arm trial of SLIT to mites. Outpatients suffering from mild allergic rhinoconjunctivitis with/without mild intermittent asthma were enrolled. All patients underwent a 1-year run-in observation in order to establish their baseline clinical conditions. After the run-in, patients were randomized to receive, in addition to drug treatment, either SLIT in tablets or matched placebo. Clinical scores (symptoms and drug intake) were recorded each year by diary card from November through February. Quality of life and satisfaction were assessed at regular intervals during the study. The study plan is shown in Fig. 1. The trial was approved by the ethical committees of the involved centres.

Patients

Adult patients (18–50 years) of both sexes were enrolled. They had to suffer from mild persistent rhinitis according to ARIA guidelines with/without mild intermittent asthma according to Global Initiative on Asthma (GINA) guidelines (17) since at least 2 years. They had to have a skin positivity to house dust mite (wheal diameter > 5 mm) (18) and a CAP-radioallergosorbent class II or greater. Exclusion criteria were: (i) systemic immunological disorders; (ii) malignancies; (iii) diabetes; (iv) chronic heart failure or chronic obstructive pulmonary disease; (v) pregnancy or lactation; (vi) skin test positivity to cat/dog dander or *Parietaria* (this latter allergen is almost perennial in the Mediterranean area); (vii) any specific IT course in the last 5 years and (viii) major psychiatric disorders. All patients signed an informed consent at the time of enrollment. A physician was always available at each centre for phone contact. All patients were instructed, as routinely done, to carry on allergen avoidance: use of impermeable mattress and pillow covers, removal of moquettes, carpets and curtains, hot water washing of bedding once weekly.

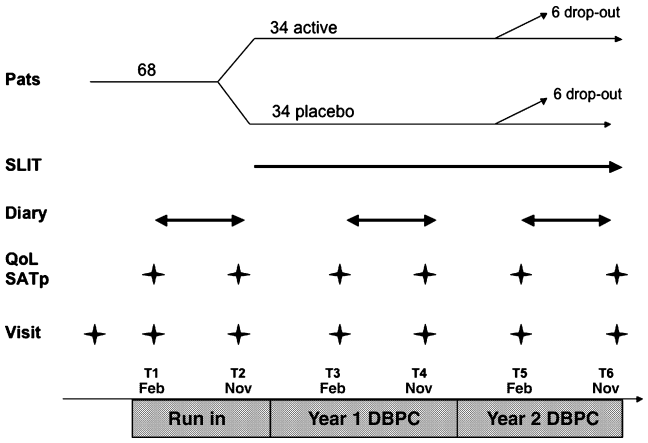

Figure 1. Study design.

Immunotherapy and concomitant medications

Sublingual immunotherapy was a monomeric carbamylated allergoid (Lais®) kindly provided by Lofarma S.p.A. (Milan, Italy) biologically standardized (9, 19) in allergenic units (AU), and prepared as soluble tablets. The tablets had to be taken in the morning on an empty stomach, and kept under the tongue for 1–2 min until dissolution before swallowing. During the build-up phase of about 1 month, tablets with increasing dosages (25, 100, 300 and 1000 AU) were used in order to gradually achieve the maximum dose of 1000 AU. Subsequently, that maintenance dose of 1000 AU was administered two times a week for 2 years continuously. Concerning the content of major allergen, it is not reported on the product label because the chemical modification of the allergen does not allow its titration in micrograms. Placebo tablets contained the same excipients without the allergoid and were undistinguishable in aspect, flavour and dissolution time from the active treatment. Patients were randomly allocated to SLIT or placebo according to a computer-generated list.

During the study, all patients were allowed to use rescue medications for symptom control: cetirizine tablets (10 mg; once daily), inhaled albuterol (100 μg; 2–4 puff on demand), intranasal fluticasone (50 μg; 1 spray per nostril once daily on medical prescription). In the case of severe rhinitis unresponsive to the standard treatment, a short course of systemic steroid was given (prednisone 50 mg daily for 3 days).

Clinical evaluation

Patients were required to record daily on a specific form the presence and severity of symptoms and the amount of medications used. The diary had to be filled from November to February, when the exposure to indoor mites is expected to be greater, for 3 years (1 year run-in and 2 years of double-blind study). The following symptoms were considered: nasal itching, obstruction, rhinorrhea, sneezing, ocular itching, cough and shortness of breath. A score ranging from 0 (absent) to 3 (severe) was attributed daily to each of the mentioned symptoms. A mean daily score was calculated for each 4-month period. The drug intake was scored 1 point for each actuation of salbutamol, 2 points for each dose of antihistamine, nasal or inhaled steroid, 3 points for each dose of systemic steroid, and a cumulative drug intake score was obtained.

All patients were also required to record on a separate diary any untoward effect, possibly related to the intake of SLIT. Adverse events were subdivided into local (oral itching, swelling of tongue) and systemic: asthma, rhinitis, urticaria, abdominal pain/diarrhoea and anaphylaxis. Finally, patients had to record the number of extra visits (other than the scheduled ones) attended, and the working (school) days missed because of their allergy problems.

Quality of life and satisfaction profile

At the beginning and the end of each observation period (November and February), patients had to fill two generic questionnaires, one assessing the health status and the other one assessing the subjective

satisfaction. The QoL was measured by the Short Form (SF)-36 Health Survey, a generic, widely used questionnaire, already validated in allergic respiratory disease. It consists of 36 items corresponding to eight domains: physical function, role limitation (physical), bodily pain, general health, vitality, social function, role limitation (emotional) and mental health. An additional question investigates a general evaluation of perceived changes in health status in the past year. The satisfaction was evaluated by the SAT-P, a nondisease specific tool with 32 questions about several aspects of daily life. The patients indicate their subjective satisfaction on a 10 cm visual analogue scale, from 0 (extremely dissatisfied) to 10 (extremely satisfied). The SATisfaction profile (SAT-P) provides an analytic score about the 32 items and a score about the five factors extracted: psychological functioning, physical functioning, work, sleep/eating/leisure and social functioning. The SAT-P has been previously used in patients with allergic diseases (16, 20).

Statistical analysis

The nonparametric tests for two independent samples are useful for determining whether or not the values of a particular variable (i.e. total symptom score) differ between two groups (SLIT *vs* placebo). This is especially true when the assumptions of the *t*-test are not met. We used the Mann–Whitney and Wilcoxon statistics to test the null hypothesis that two independent samples came from the same population. Their advantage over the independent samples *t*-test is that Mann–Whitney and Wilcoxon do not assume normality and can be used to test ordinal variables.

Results

Patients and drop-outs

Sixty-eight patients were enrolled in the trial. Their mean age was 31.28 ± 8.14 years, with an age range of 18–49, and 41.2% of them were male. Twelve patients, six in each group, dropped out, mainly during the run-in phase. Two subjects from the placebo group withdrew for concomitant illness, nine patients (four placebo and five active) retired their informed consent for personal reasons and one active patient dropped out for major protocol deviation (unattended visits). Fifty-six patients (mean age 32.14 ± 7.97 years, 39.3% male) completed the study. The patients were homogeneous at baseline for demography and clinical characteristics (Table 1).

Clinical parameters

Due to the very long duration of the study, a rate of $<15\%$ of missing data in the clinical diaries was considered acceptable. Fig. 2 shows the mean daily clinical score (all symptoms) at baseline, after 1 and 2 years of treatment. A significant difference between the two groups could be found after 1 year of treatment ($P = 0.027$), whereas no statistical difference was found at the second year, although a trend towards improvement was seen. Concerning the symptom 'nasal obstruction' a significant difference between groups was present after 1 year ($P = 0.05$) and 2 years ($P = 0.033$) of treatment (Fig. 3). No difference during the study could be found for the other symptoms taken separately. The global drug intake is shown in Fig. 4, being the difference significant at the first year of treatment ($P = 0.036$), but not at the second, although a trend toward difference was

Table 1. Demographics and clinical characteristics by treatment group

	SLIT	Pla
N	28	28
Mean age	30.64	33.64
Age range	18–49	19–49
Sex (M/F)	11/17	11/17
Rhinitis (%)	82.1	71.4
Rhinitis + asthma (%)	17.9	28.6

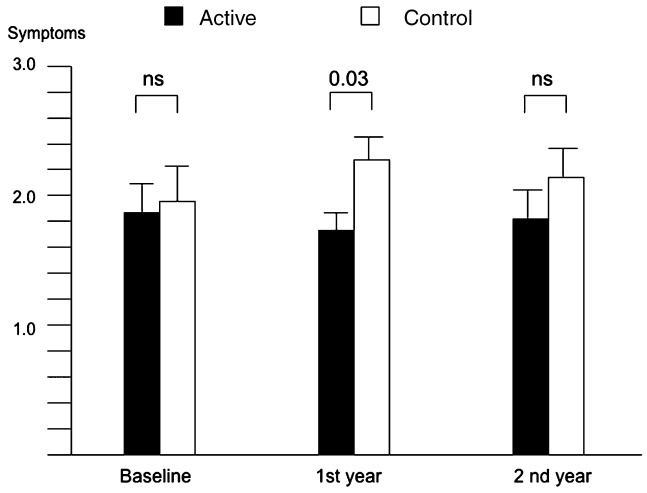

Figure 2. Mean ± SD daily total symptom score in the active and placebo group at baseline and after 1 and 2 years of treatment.

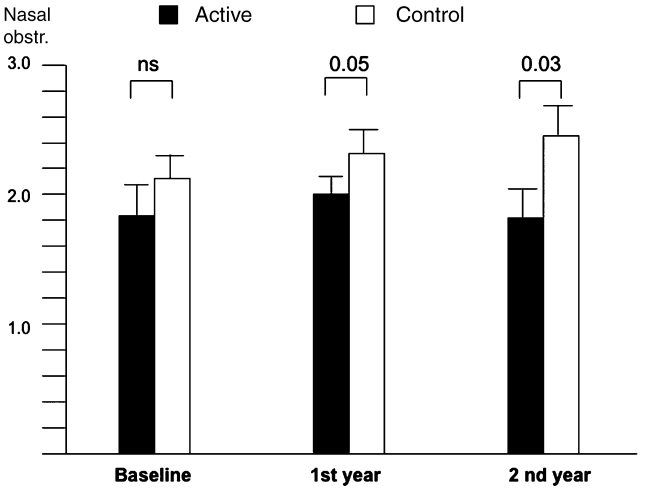

Figure 3. Mean ± SD daily obstruction score in the active and placebo group at baseline and after 1 and 2 years of treatment.

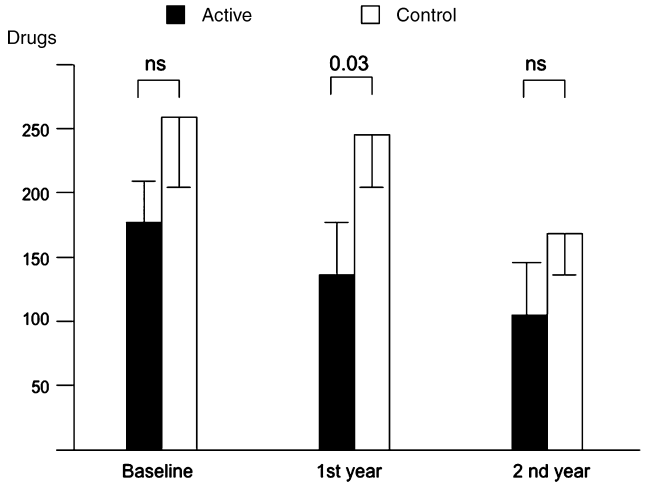

Figure 4. Mean ± SD of the drug intake in the considered 4-month period.

seen. Nasal steroids were prescribed only occasionally in both groups and a statistical analysis was not therefore possible.

The occurrence of adverse events was not significantly different between the two groups. Thirty events (11 patients) in the actively treated and 43 events (16 patients) in the placebo group were reported and none was judged possibly or certainly related to treatment. A list of those adverse events occurring at least twice is shown in Table 2. In the active group, two patients reported transient oral itching and one patient mild abdominal pain.

Table 2. Detail of the adverse events occurring more than one time

	Active	Placebo
Cough	2	5
Asthma attack	10	12
Rhinitis	5	3
Flu-like syndrome	5	12
Otitis	3	4
Traumatic fracture	2	1

Quality of life, satisfaction profile and pharmaco-economics

There was no statistical change in all the domains of the SF-36 questionnaire at the six timepoints, and all the scores were quite high. Table 3 shows the values for each domain that are not different from those of a reference healthy population (21–23). There was indeed a difference between the active and the placebo group in the only item 'overall change in health status' ($P = 0.05$) after the second year of treatment (Fig. 5). No change in the items of the SAT-P questionnaire was found, because in this case also the scores were always comparable with those of a healthy reference group (data not shown).

There was a significant difference between the two groups as far as the pharmaco-economic aspects are concerned. No working absence was reported in the active group. In the placebo group, three patients reported a total of 22 working days lost attributable to their allergic disease. This means a cost of 3047€ (138.5€ per day) (24) that is superior to the cost of SLIT for the same number of patients (about 2700€). Moreover, 12 patients (43%) in the placebo group and six patients (25%) in the active group needed one or more extra visit ($P = 0.01$) due to illness exacerbation.

Discussion

The use and indication of SLIT in mite allergy are less defined than in pollinosis. In fact, the results of clinical trials are less apparent in term of efficacy and need longer times to become measurable. Some clinical trials have provided positive results (9–11, 25), whereas in other studies the effects were marginal (26) or absent (27, 28). This may be due to the fact that with mites the allergenic exposure is extremely variable during the course of the year and therefore, prolonged periods of observation are needed. Furthermore, mite-induced allergy may provoke less severe symptoms, although long-lasting. It is difficult to carry out studies with mite allergy in adult patients. In fact, it is objectively difficult to keep many patients on a double-blind design, recording symptoms and drug intake

Table 3. Short Form-36 domains score at the six timepoints in the active and placebo group

	T1		T2		T3		T4		T5		T6		
	SLIT	Pla	SLIT	Pla	SLIT	Pla	SLIT	Pla	SLIT	Pla	SLIT	Pla	Ref
Physical function	90.67	90.77	91.43	92.50	93.66	90.00	92.50	93.19	96.30	92.69	90.00	93.40	84.46
Role physical	87.96	85.00	83.93	83.00	87.04	92.00	84.62	85.23	87.50	86.54	81.25	93.00	78.21
Bodily pain	81.61	73.73	81.00	74.70	88.15	77.76	86.00	73.69	96.18	72.81	83.79	80.52	73.67
General health	67.63	60.32	67.93	61.44	69.08	60.68	67.12	66.00	67.21	64.67	71.77	67.93	65.22
Vitality	60.93	61.54	59.07	58.27	57.50	56.27	56.15	59.17	58.57	56.15	55.77	61.99	61.9
Social function	75.00	67.31	80.36	73.61	75.00	70.00	81.48	77.88	79.12	75.46	75.45	75.93	77.43
Role emotion	88.89	80.00	86.90	84.62	88.89	90.28	87.04	88.41	90.12	80.77	84.52	83.33	76.16
Mental health	69.04	68.15	68.89	70.22	69.88	67.44	69.38	69.67	72.29	68.31	70.77	73.12	66.6

The last column on the right shows the mean values for a reference healthy population (19).

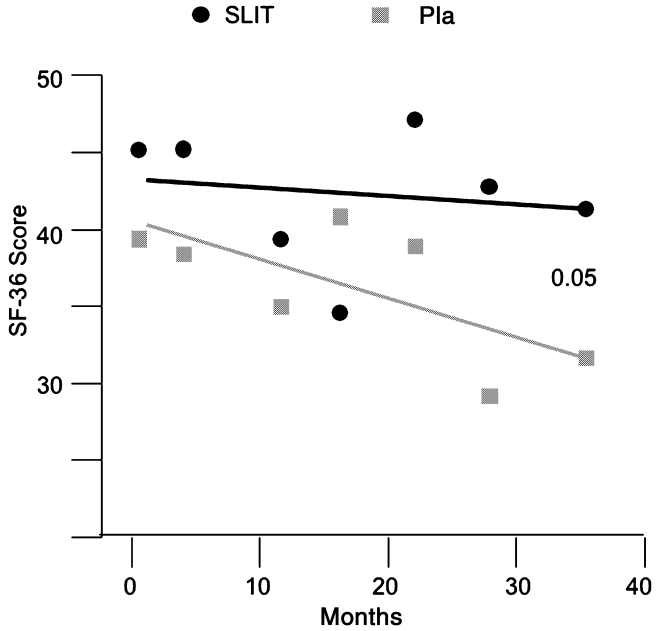

Figure 5. Short Form-36 scores 'change in health status' measured up to 36 months.

continuously for years. We therefore chose to record the clinical scores only 4 months a year, from November to February, when the exposure to allergens was expected to be higher. With this method, we could demonstrate that allergoid SLIT induced a significant improvement of total clinical symptoms and drug consumption at the first year, whereas in the second year no significance was reached. This is consistent with the fact that all patients had a mild disease, and were allowed to use rescue medications for their symptoms. On the other hand, the symptom 'nasal obstruction' that is the most bothering symptom of persistent rhinitis, especially in patients allergic to perennial allergens like mites, was improved in both the observation periods. Obstruction in persistent forms is largely sustained by inflammation, and the improvement of obstruction is consistent with the previously demonstrated anti-inflammatory action of the allergoid IT (9). The nonsignificant difference between the two groups at baseline did not affect the final results as confirmed by a time-trend analysis.

Concerning QoL, all patients had QoL profiles not different from a control group of healthy subjects (15, 21–23), so it was not conceivable to obtain an improvement of normal values. Thus, we can deduce that a mild disease does not significantly affect the QoL of patients or, in other words, patients with mild symptoms cope with their disease and do not perceive an impact on daily functioning. This fact, indirectly confirms the validity of the ARIA classification of the severity of rhinitis. In addition, it has been previously shown that generic questionnaires (e.g. the SF-36) may be unable to detect changes in health status (29). On the other hand, a significant change in the item exploring the variation of the disease's status was found and a statistical projection showed that this change would have been maintained and would have become more and more significant in the next years. Of note, there was also a difference in extra visits and working absence in the active group, this indirectly testifying that a general effect on the disease severity has occurred. It remains to be ascertained whether a continuous SLIT treatment in mild disease can be proposed to all patients in clinical practice, although the adherence to treatment was shown not to represent a problem (30).

The clinical effect of SLIT also in mild disease should be considered in the light of the very favourable tolerability profile that would also allow small children to be safely treated (31). In this study, the safety aspect was further ensured by the use, as active principle, of a monomeric carbamylated allergoid, which has a reduced IgE-binding capacity. The monomeric carbamylated allergoid resulted to be very suitable for SLIT treatments because on the one hand its low molecular size (19) allows absorption at the mucosal level and on the other, the carbamylation improves its bioavailability by increasing the resistance to enzymatic degradation at the gastrointestinal level, as shown by biodistribution studies performed with the radiolabelled Der p 2 (32). In conclusion, SLIT with carbamylated allergoid exerts a measurable clinical effect even in mild rhinitis due to mites, and favourably affects the pharmaco-economic profile of the disease.

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