

SAFETY AND EFFICACY EVALUATION OF SUBLINGUAL ALLERGEN-SPECIFIC IMMUNOTHERAPY A RETROSPECTIVE, MULTICENTER STUDY

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In recent years, several controlled studies have proved the efficacy and safety of sublingual specific immunotherapy, as a possible alternative to the classic subcutaneous route of administration. This alternative option has been officially confirmed by the recent WHO position paper "Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases". Since sublingual immunotherapy has now been widely used for years, we carried out an open, multicentric, retrospective study to investigate the efficacy and safety of this form of treatment in a large number of patients. To this end, we studied 302 subjects undergoing sublingual immunotherapy for at least three months with different allergen compositions. Notwithstanding the obvious limitations due to the study design, this survey has confirmed the high efficacy and safety of this form of treatment, as already reported in previous controlled studies. Sublingual immunotherapy appears to be a simple, well-tolerated and effective method of treatment of allergen-specific diseases.

Numerous randomized trials have shown the efficacy of allergen immunotherapy in treating allergic asthma (1) and allergic rhinitis, either due to pollens or perennial allergens, such as mites or animal danders (2). In recent years, the safety of this treatment has been cause of major concern, in that serious, albeit rare, systemic reactions were reported after allergy injections (3,4). Although official documents have confirmed the safety of this treatment, when administered in compliance with international guidelines, alternative forms of immunotherapy have nonetheless been considered in an effort to identify a safer route of administration

than the traditional subcutaneous therapy. In this regard, sublingual immunotherapy (SLIT) appears to be particularly promising, in terms of safety, efficacy and compliance (5-8).

In controlled clinical studies SLIT has been shown to be effective in reducing symptoms, medications scores and responses to provocation tests in patients allergic to mites (9-11), pollens (12-19), cat (20,21) and molds (22), although more studies are clearly required that may at least match the large number of controlled trials performed in the past years with the traditional injection therapy. Furthermore, in two studies

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comparing SLIT with injection therapy, results were shown to be comparable, and in another study even superior to the traditional subcutaneous therapy. (22-24)

All these studies also demonstrated that SLIT is easier, inexpensive, and safer to perform than subcutaneous therapy, as confirmed by a large post-marketing surveillance study conducted in Spain in 1995. (25)

In light of the above evidence; the recently published WHO Position Paper approved by the leading Scientific Societies, stated that SLIT "may be a viable alternative" to the traditional subcutaneous therapy. (26)

In Italy, SLIT has been largely prescribed for several years. In this study, we carried out a clinical retrospective analysis in 302 patients treated in 7 different Allergy Departments regarding the efficacy and safety of SLIT, as judged by patients and treating physicians.

MATERIALS AND METHODS

Patients

The study was an open, retrospective, multicenter analysis carried out on 302 patients treated with SLIT for at least 3 months in seven different Allergy Centers. Patients mean age was 20,8 years (min 2, max. 68). Children up to 12 years of age were 114 (37.7 %). Of the 302 patients, 171 were males and 131 females. Rhinitis was reported as the most severe symptom by 134 subjects (44.4 %), asthma by 92 patients (30.5 %), dermatologic symptoms by 47 (15.6 %) and ocular symptoms by 29 patients (30.2 %). Previous immunotherapy had been received in the past by 31 patients.

Allergen extracts

Hydroglyceric standardised extract solutions (Allergopharma, Reinbek, Germany and Bracco, Milan, Italy) were employed. Treatment consisted of 3 vials containing 100 TU/ml, 1000 TU/ml, 10.000 TU/ml respectively. Maintenance therapy was conducted using further vials of the higher concentration.

Treatment

The 302 patients were treated with the extract compositions summarized in Table 1.

At the time of this retrospective study 256 treatments were still ongoing (84.8 %). The average duration of treatment was 18 months (min 3, max. 46). A total of 90 patients had been treated up to 13 months (29.8 %), 153 from 13 to 24 months (50.7 %) and 59 for longer than 24 months (19.5 %).

SLIT was performed with a perennial maintenance schedule also with pollen extract. Maintenance therapy was carried out with 7 drops of the higher concentration vial taken 3 times a week.

Patients were instructed to sublingually maintain the drops for 3 minutes, then to swallow.

Retrospective investigation

A questionnaire was sent to the Allergy Departments, including a detailed past and allergic history of the patients, the state of the immunotherapy, the characteristics of adverse events, if any, and a physician judgement about the clinical efficacy, the drug consumption and the tolerability of the treatment. Information about patients compliance were also requested.

Data were stored and analysed in a Data Base (Access 2).

RESULTS

Treatment efficacy

At the time of the study, 293 patients (97.0%) reported a clinical improvement; out of these patients, the clinical condition was defined as "better" by 152 subjects, and "definitely better" by the remaining 141. 7 patients (2.3%) were unchanged while the clinical condition of the remaining 2 patients was unknown. These data were obtained only by a subjective evaluation in 180 pts, while 119 subjects filled a symptom score; in 3 patients the method of evaluation was unknown. The 7 "unchanged" patients had been treated for less than 24 months: no clinical failure was reported in the 59 subjects treated for more than 24 months. Table 2 summarize the treatment efficacy with regard to the length of treatment.

The clinical efficacy was also very good in the group of 114 children up to 12 years of age: an overall improvement was reported in 108 subjects (94.7 %). No difference was observed according to extract composition: SLIT was effective in 96.2 % of the patients treated with mite and grasses

extracts (159 and 78 respectively) and in 98.3 % of 58 subjects allergic to parietaria. Although not significant, clinical failure was slightly more frequent in patients treated with mite extracts (5 cases, 3.1 % of mite patients). Table 3 shows the efficacy of treatment with regard to extract compositions.

Clinical results were also comparable among different symptom presentations: SLIT was effective in 96.2 of the patients with predominant asthmatic symptoms, 96.4 of subjects with rhinitis, 100% of patients with conjunctivitis and 98.0 % of patients treated for dermatologic problems.

Drug consumption. A reduction in medications use was reported by 296 patients (98 %), with a very marked reduction observed in 141 subjects (46.6 %). 4 patients reported no changes in drug consumption, while this data was not available in 2 cases.

Treatment safety and tolerability

The tolerability of SLIT was reported as "good" or "very good" by 99.3 % of the patients (300 subjects), and reached 100 % in the group of 114 children up to 12 years of age. The tolerability was "mediocre" in 1 patient, "poor" in another 1 and "unknown" in a third subject. Only 3 patients (1 %) reported an adverse systemic reaction during the treatment: one patient had a mild asthma, the other two had a moderate cough. The reactions were successfully treated with β_2 -agonists and disappeared within few hours. All the patients were able to continue the treatment without further reactions. Table 4 reports the tolerability in children, according to different groups of age.

Compliance

The recommended top dose of 7 drops of strength 3 has been reached by all the patients (302 subjects) and has been taken 3 times a week, as prescribed. 11 patients did not take the drops as

No of Pts	Extract composition	%
159	Mix mites	52.6
78	6-grasses mix	25.8
58	Parietaria	19.2
5	Mix grasses/parietaria	1.7
2	mix of birch/alder/hazel	0.7

Table I. Extract compositions.

Clinical condition	< 13 months	13-24 months	>24 months
Definitely better	37	80	24
Better	47	70	35
Unchanged	4	3	0
?	2	0	0
Totale	184	153	59

Table II.

Treatment efficacy with regard to the length of treatment.

Composition	CLINICAL CONDITION			
	Definitely better	Better	Unchanged	?
Grasses	39	36	1	2
Parietaria	22	35	1	0
House-dust Mites	76	78	5	0

Table III.

Treatment efficacy with regard to extract compositions.

TOLERABILITY	0-4 yrs	5-9 yrs	10-12 yrs
Very good	1	40	22
Good	5	24	22
Poor	0	0	0

Table IV.

Tolerability in children.

regularly as recommended: 3 subjects because of symptoms of asthma, 2 because of intercurrent pneumonia, 1 because a nasal surgery, 1 for an infection and 1 for unknown reasons; 3 patients were just poor compliant. 9 patients had to start again with a new initial treatment.

DISCUSSION

This study obviously entails all the limitations of retrospective uncontrolled studies, and a number of results must be interpreted with caution. Nevertheless, interest in alternative routes of specific immunotherapy has been growing in recent years, and the WHO document, as reported, concludes that SLIT may be a viable alternative to the traditional injective therapy (26): for this reason, we believe that all sorts of observations may assist in more clearly defining the possibilities of this form of treatment. We also agree that "more immunotherapy clinical studies are needed" (27) if we want allergists to be able to rely not only on the results of DBPC studies carried out in a limited population, but also on information about efficacy and safety of treatments in larger surveys.

The present study can be viewed as a practical extension of all the above-mentioned controlled studies that have already demonstrated the safety and efficacy of sub-lingual specific immunotherapy.

First of all, this study confirmed the high safety and tolerability of SLIT in a large number of patients, a result that cannot be challenged by the lack of a control group: only 3 patients out of 302 reported a mild reaction, and no patient had to withdraw from the treatment. The high tolerability in the group of 114 children under 12 years of age is especially noteworthy, as children could be one of the main targets of SLIT, being it a painless, safer and definitely more acceptable form of treatment than injection therapy. What's more, 70 of these children were under 9 yrs of age.

It is crystal-clear that the exceptional safety of a treatment is meaningless if it is not associated with significant clinical efficacy. In this study, the clinical results were defined as "very good" or "good" in 293 out of 302 subjects (97%), as judged by patients themselves or by treating physicians. Furthermore, 296 patients (98%) reported a decrease of drug consumption. Data on clinical results must of course be interpreted with more caution, due to

the retrospective design of the study, the lack of a control group and the well-known high incidence of placebo effects in the anti-allergic treatments. Moreover, the very high percentage of observed positive results could also raise the doubt of potential data overestimation.

Nevertheless, our results indicating SLIT efficacy are fully in line with conclusions from a large number of previously published DBPC studies. The more recent studies have shown a significant decrease of symptom and medication score in 70 patients treated with grass pollen for one season (15); a marked reduction in skin and conjunctival response, along with the rhinomanometry, in 20 patients treated for four months with birch pollen (16); a reduction of symptom score and skin test reactivity in 34 children treated for 2 years with olive pollen (18); a significant decrease of symptom score and skin reactivity, along with an increased threshold dose for conjunctival provocation tests, in 20 children treated for 2 years with *Parietaria* extracts (19); a significant decrease of local inflammatory reaction with conjunctival provocation test in patients treated with mite extract. (11)

Given that all the controlled studies demonstrate the high efficacy of this treatment, it should not be surprising that a retrospective, open study in a large number of patients could also lead to the same conclusions.

These results demonstrate that SLIT is a valid and safe method to treat respiratory allergies. This route of administration could be initially reserved to patients for whom the traditional injection therapy is not indicated (small children, patients living far away from allergy centers, people at risk of systemic reactions) or could be prescribed as a maintenance therapy after 2-3 years of successful injection therapy. However, the results of all the studies suggest that in the near future sublingual immunotherapy could also be prescribed as a treatment of first choice.

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