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SPECIFIC IMMUNOTHERAPHY OF ALLERGIC DISEASES: A THREE YEARS PERSPECTIVE OBSERVATIONAL STUDY

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In order evaluate the long-term benefit of Specific ImmunoTherapy (SIT), administered either subcutaneously or sublingually, in comparison with drug therapy, in terms of efficacy, tolerability and patients' adherence to the treatment, a three years perspective, observational study was carried out in a rather large number of allergic subjects. One hundred and ten patients of both sex (50F, 60M; age: 22.4 - 35.5 years) were admitted. Sixty of them were rhinitics, some with concomitant mild intermittent asthma or conjunctivitis; 43 had a persistent asthma, often with concomitant rhinitis. Seven had urticaria. Sixty patients were treated with the sublingual allergoid SIT (in tablets) plus drugs on demand, 19 with the subcutaneous SIT (depot, aluminium hydroxide subcutaneous SIT) and 31 with the pharmacological therapy alone, mainly nasal steroids and antihistamines. The treatment efficacy, evaluated after 36 months, by symptoms and drug consumption reduction, was statistically better in the group from the allergoid sublingual SIT than in the other two groups. This was the case also for the tolerability, the patient's compliance and the physicians' and patients' opinion. The present findings, obtained by a non-randomized study, show that the sublingual allergoid SIT was very appreciated by both patients and physicians for the good effectiveness and the high degree of safety guaranteed, in addition to its simplicity of use.

The prevalence of allergic disease has been increasing dramatically in the last three decades, especially in the industrialized western countries, with all the related social and economic consequences in term of absence from work, costs for the purchase of medicines, medical visits, hospital admissions and deterioration of the patient's quality of life (1,2).

Many efforts have been made by public health organizations to reduce this phenomenon, through primary preventive measures. The results of these initiatives have not always been entirely satisfactory (3). However, once the subject begins to manifest the first symptoms of the disease, it is absolutely necessary to implement a secondary prevention strategy to prevent its progression (3). Thus far, the only treatment considered able to modify the natural course of allergic disease and to avoid or at least to slow the development of asthma in patients with allergic rhinitis is specific immunotherapy (SIT) (4), although some pharmacological therapies, i.e. the new-generation intranasal steroids and antihistamines would seem to have some preventive efficacy, if taken during childhood to treat the rhinitic symptoms (5).

MATERIALS AND METHODS

Design

The study was a perspective, observational, not randomized, 36 months follow-up study, conducted

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over the years 1997-2000. This kind of design was chosen for its similarity to the "true every day" clinical practice and the possibility of enrolling a more diversified outpatient population.

The patients, once included in the study, were divided into three groups according to their own choice. The first and the second group were treated, respectively, with either sublingual allergoid or subcutaneous SIT plus pharmacological therapy on demand while the third group received only the pharmacological therapy.

Patients

One hundred and ten patients of both sex (50F; 60M) with an age ranging from 22.4 to 35.5 years were included in the study after a normal diagnostic allergological work-up. Most of the patients were rhinitics (n=60), and some also had concomitant mild intermittent asthma or conjunctivitis. Others (n=43) had a persistent asthma: most of them with concomitant rhinitis, a few patients were only asthmatic. A small percentage had urticaria (n=7). The main allergens involved were: *Dermatophagoides*, *Parietaria*, *Graminaceae* and *Olea*.

Treatment

Sixty patients were treated with a sublingual monomeric allergoid, (LAIS® tablets Lofarma S.p.A., Milan) and drug therapy (see below) on demand. An allergoid is an allergen that has been chemically modified in order to reduce its allergenic power. Of these, 29 were allergic to *Dermatophagoides*, 24 to *Parietaria*, 5 to *Graminaceae* and 2 to *Olea*. The tablets were placed under the tongue, dissolved in the mouth for 1-2 minutes, and then swallowed. The build-up phase involved the administration of increasing doses of the allergen (usually 25 AU, 50 AU, 100 AU, 300 AU and 1000 AU). Each dose was taken, on average, for 3 alternate days. In the maintenance phase, most patients received 2000 AU twice weekly.

Nineteen patients received the subcutaneous SIT (depot, aluminium hydroxide subcutaneous SIT, Lofarma S.p.A., Milan) and, if needed, the drug therapy. Of these, eleven were allergic to *Parietaria*, 5 to *Dermatophagoides* and 3 to grass. Also the subcutaneous SIT was administered in two steps: each patient started with a build-up phase that was followed by a maintenance phase. For *Dermatophagoides* and *Parietaria*, which is almost a perennial allergen in Sicily, we employed a perennial administration schedule. For pollens a pre-seasonal scheme was used.

Finally, the remaining 31 patients were treated only with the pharmacological therapy, mainly topical steroids and antihistamines. Among these patients, 15 were allergic to *Dermatophagoides*, 9 to *Parietaria*, 4 to *Graminaceae* only, 1 to *Olea* only and 2 to *Graminaceae* and *Olea*.

The specialist completed, for each patient in the three groups, a chart describing the patient's characteristics. Each patient completed a questionnaire at the end of treatment.

The specialist had to express a judgement about efficacy, tolerability and adherence to the treatment while patients were requested to judge the treatment in relation to the following items: symptoms, drug consumption, school days off and work days lost, hospital admissions, preferred treatment (either sublingual or subcutaneous SIT or drugs) and satisfaction degree. All questionnaires were analyzed and the final data were evaluated after 36 months of treatment.

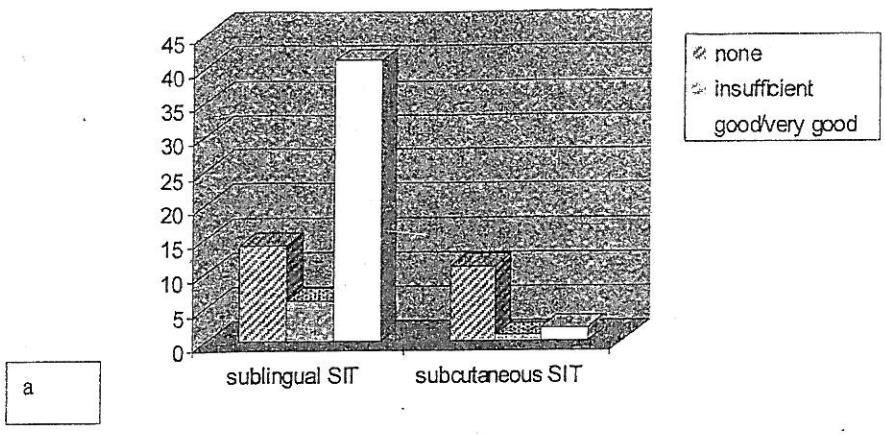
Statistical analysis

In line with the main international references on this topic, we assessed the results of this observational program after patients had been treated for three years. A descriptive, non-parametric approach was taken for the main demographic variables.

The three therapy schedules were compared, according to the above mentioned criteria, with the chi-squared test.

RESULTS

Eight patients interrupted the immunotherapy during the study period, for reasons unrelated to the SIT: 3 while taking the sublingual monomeric allergoid and 5 with the depot subcutaneous therapy. One patient because of occurrence of pregnancy after the beginning of SIT, 2 patients because of poor adherence to the treatment, 2 patients because of the occurrence of flu during SIT. As a result, 102 patients were evaluated. When the two kinds of SIT were compared, the physician's opinion was particularly in favor of the sublingual



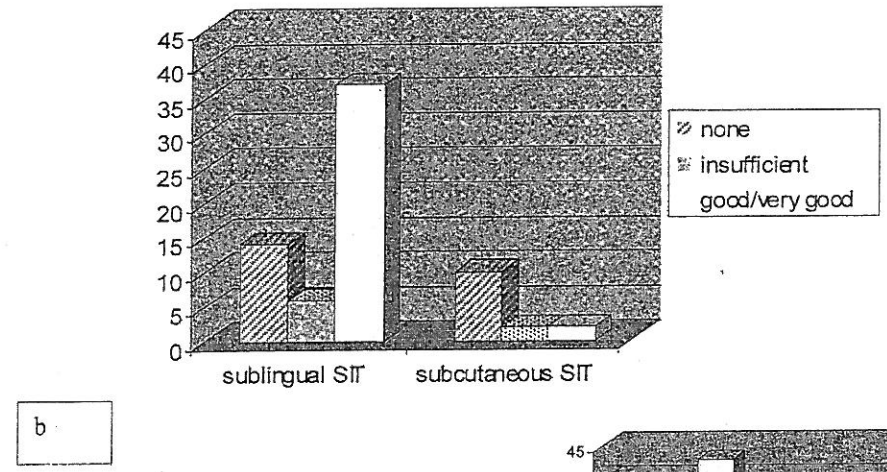
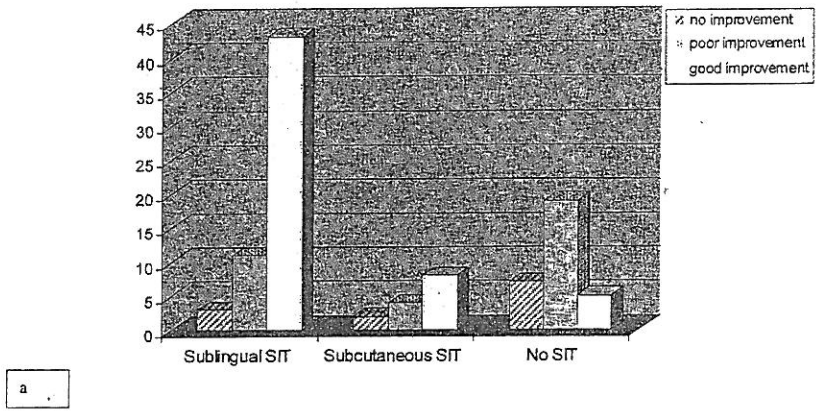


Fig. 1. *Physician's opinion on efficacy: (a) symptoms, (b) drug consumption.*



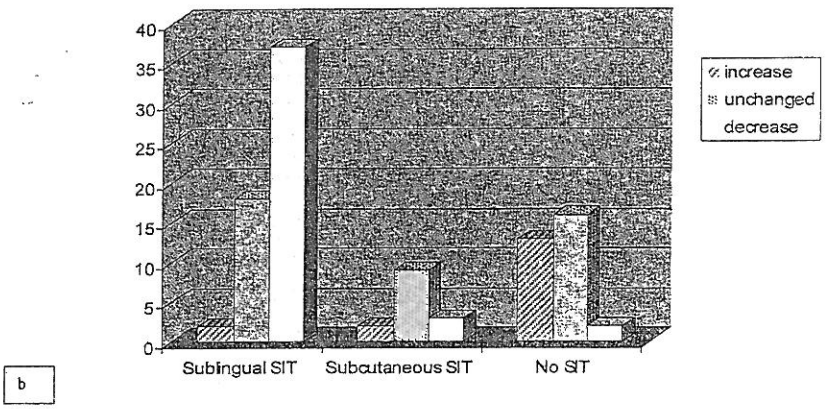


Fig. 2. *Patient's evaluation on symptoms (a) and drug consumption (b) after treatment.*

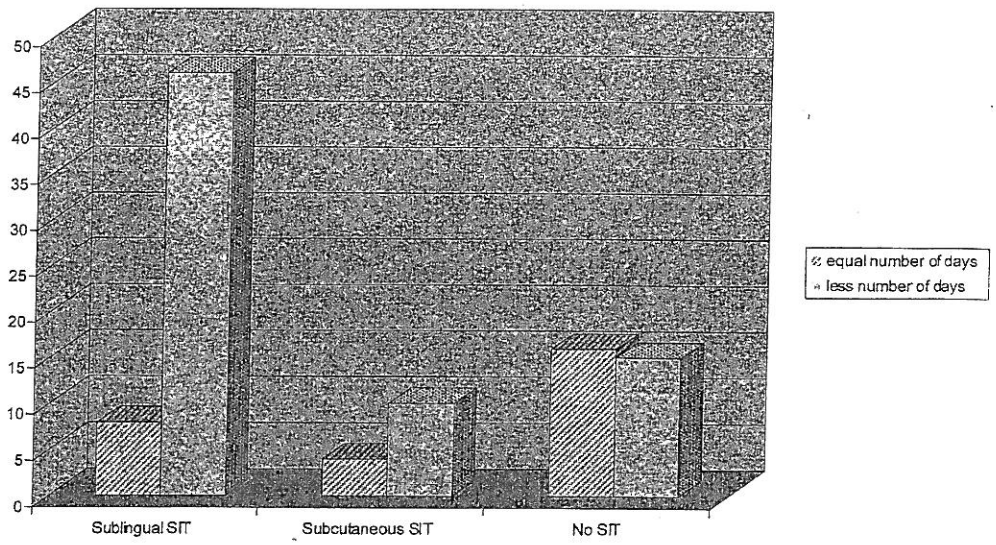


Fig. 3. *Comparison between the school and work days lost before and after treatment.*

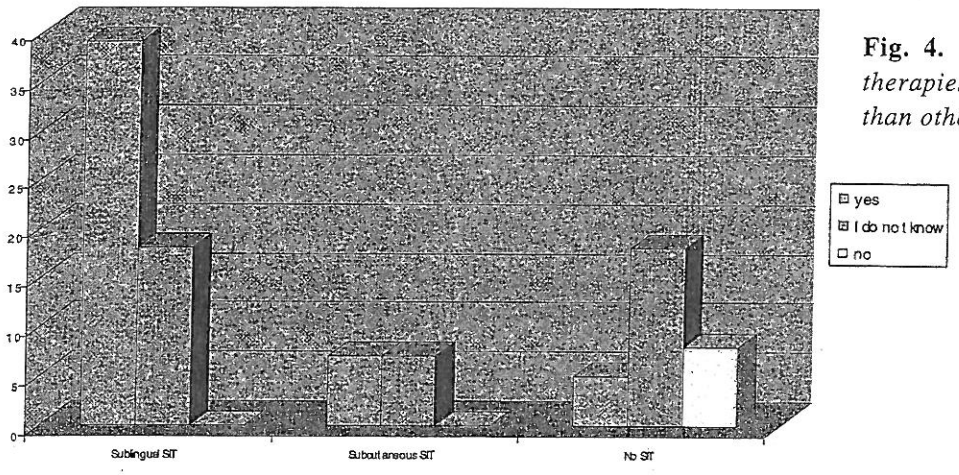


Fig. 4. *Patient's judgement on therapies: is sublingual SIT better than other treatments?*

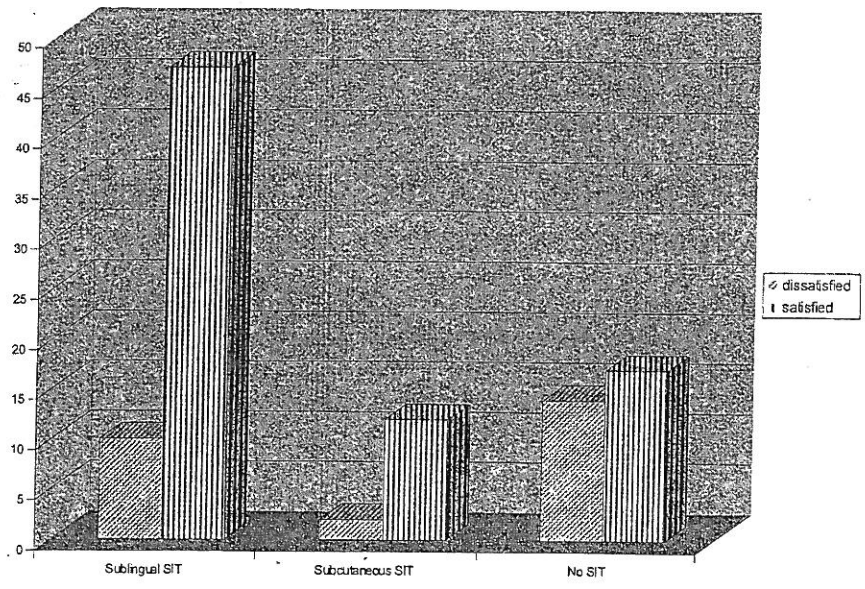


Fig. 5. *Patient's degree of satisfaction of treatments.*

allergoid form of therapy, both as far as the tolerability and the adherence to the treatment were concerned. The same opinion was expressed for the efficacy as well, both based on symptoms and drug consumption reduction. All these different physicians' opinions concerning the two forms of SIT were statistically significant point of view ($p< 0.0001$) (Fig. 1).

Also the opinion expressed by the patients through the filling in of the questionnaires was firmly in favor of the SIT and in particular of the allergoid sublingual form. When the drug consumption was analyzed, the best therapeutic option was again the sublingual monomeric form. As far as the symptoms reduction is concerned, the same results were observed (Fig. 2). This was also the case when the number of school days off, or the lost working days were taken into consideration (Fig. 3). Moreover, the sublingual allergoid SIT was considered by the patients to be "better than the other two therapies" (Fig. 4).

Also the patients' degree of satisfaction at the end of treatment was high, for both the forms of SIT (Fig. 5). Furthermore, very few patients declared themselves dissatisfied with these therapies. Lastly, the difference between the patients' opinion on the sublingual SIT in tablets and that expressed about the other two treatments was highly significant from a statistical point of view as well ($p< 0.0001$).

DISCUSSION

The results of the present long term, perspective, observational study confirm conclusions from most of the previous studies, both observational (1) and randomized placebo-controlled, published on sublingual SIT during the last ten years (7-10). The allergoid sublingual SIT appears in fact to reduce to a greater extent both the drug consumption and the allergic respiratory symptoms due to pollens or house dust mites, when compared with the pharmacological therapy alone. Among the two different forms of SIT, the subcutaneous and the sublingual, the latter showed, in our study, to be more effective as well as more accepted by both patients and doctors. Moreover, the tolerability and the safety of the allergoid sublingual form was superior to that of the conventional one. The mechanism by which sublingual SIT works is still largely unknown, even if there are a number of possible explanations. After allergen exposure, the oropharyngeal mucosa, which might represent a potential site for the preferential induction of immunological tolerance, seems to be capable of modifying the allergic reactivity, regardless of the events that may follow swallowing of the allergen (11). The precise mechanisms by which allergen administered via the sublingual route exerts this effect remain to be defined. They seem likely to involve stimulation of allergen-specific suppressor cells in the regional lymph nodes draining the oral mucosa, with less effect on serum antibodies (11). Another possible explanation might be the development of desensitization of basophils and mast cells (8). At present, it is known that no difference in local pharmacokinetics exists between the allergen and the allergoid. No direct absorption through the oral mucosa is detectable in both cases, as it occurs mainly through the gut. However the peak plasma concentration attainable with the sublingual monomeric allergoid in tablets is significantly higher than that obtainable with the native allergen, due to its increased resistance to gastrointestinal enzymatic degradation (12).

The main limitation of the present study was the observational, non randomized design. On the other hand, its long duration (3 years) does not allow easy inclusion of a placebo arm. Keeping in mind this methodological limitation, we can conclude that, according to the study findings, the allergoid sublingual SIT was positively appreciated by both patients and physicians for its simplicity of use, good efficacy and the high degree of safety offered.

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