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Short communication

Safety of sublingual immunotherapy with monomeric allergoid in adults: multicenter post-marketing surveillance study

Background: Sublingual immunotherapy (SLIT) appears to be acceptably safe in clinical trials, but post-marketing data are needed to provide essential information. This study specifically evaluated the safety of commercial SLIT in adult patients in a post-marketing phase.
Methods: A total of 198 patients (83 male, 115 female, mean age 24.4 years) receiving SLIT for respiratory allergy were followed up for 3 years by a specific questionnaire for side-effects. SLIT (LAIS, Lofarma SpA, Milan, Italy), a monomeric allergoid in tablets, was administered, in association with drug therapy, pre- or pre-coseasonally for pollen and continuously for mites. The average duration was 12–36 months, and the total of doses was about 32 800. Side-effects were grouped as ocular, gastrointestinal, rhinitis, asthma, urticaria, edema of tongue/lips, and anaphylaxis. The severity was graded as low (no need for treatment or dose adjusting, no interference with activities), moderate (interference with activities/need for drugs/SLIT discontinuation), and severe (life-threatening/hospitalization/emergency care).
Results: Seventeen events corresponding to 7.5% of patients and 0.52 per 1000 doses were reported. Seven episodes of rhinitis (two in two patients), three of oral itching, and one of abdominal pain were self-limiting. Two cases of urticaria and two of abdominal pain/nausea were controlled by a temporary dose-adjustment, and one case of urticaria and conjunctivitis required oral antihistamines. Medical intervention was needed in six patients only during a 3-year period.
Conclusions: The results of this study, performed in a real situation of clinical practice, confirm the satisfactory safety profile of SLIT.

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Key words: post-marketing surveillance; safety; side-effects; sublingual immunotherapy.

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The clinical use of sublingual immunotherapy (SLIT) has been approved in the recent consensus statement of the World Health Organization (WHO) (1) and in the EAACI/ESPACI position paper (2). The role of SLIT as a viable alternative to subcutaneous immunotherapy is based on well-documented experimental evidence, as also noted in the new ARIA document (''Allergic Rhinitis and its Impact on Asthma'', position paper, in cooperation with WHO, forthcoming).

The overall aim and the main advantage of SLIT are the favorable safety profile. The safety of SLIT was established mainly on the basis of the cumulative data from the double-blind, placebo-controlled (DBPC) studies so far published. Indeed, although some post-marketing surveillance studies in adults and children (3–5) are now available, some skepticism about the safety of SLIT still remains (6). One of the most important concerns is about the self-administration of SLIT, which excludes the interaction between patient and physician and the direct assessment of the possible side-effects. Therefore, any new report on the safety of SLIT during its clinical use can be considered useful for further validation of its routine employment.

The increasing clinical use of SLIT in clinical practice provides the opportunity to perform direct surveys of patients taking the treatment: these surveys represent an equivalent of the classical retrospective studies performed with subcutaneous immunotherapy (7).

This study specifically aimed to evaluate the safety of SLIT in a population of adult patients in the post-marketing phase. A specific questionnaire for side-effects was used.

Material and methods

Patients and diagnosis

The post-marketing surveillance study was conducted in the following three Italian centers: the Allergy and Respiratory Unit,

S. Orsola Hospital, Brescia; the Allergy Unit, Desenzano Hospital; and the Department of Allergy and Respiratory Diseases, University of Genoa.

A total of 198 consecutive outpatients (83 male and 115 female, mean age 24.4 years, age range 15–51 years) were prescribed SLIT for respiratory allergy, and they were subsequently followed-up to determine the safety of the treatment. Their demographic data are shown in Table 1.

SLIT was prescribed according to the general WHO criteria (1), including a detailed diagnosis, the assessment of the causal role of the allergen, and the cost/benefit ratio aspect. A positive history of perennial or seasonal rhinitis and/or mild asthma and skin prick test positivity to specific allergens were always required. The skin test standard panel (Lofarma S.p.A., Milan, Italy) included: mites, *Parietaria*, grasses, olive, birch, cat and dog dander, molds, and Compositae. In the case of multiple sensitization, a nasal or conjunctival challenge was performed in order to detect the relevant allergen. No patient had the following contraindications: beta-blocker intake, malignancies, immunodeficiencies, upper respiratory abnormalities, chronic obstructive pulmonary disease, major psychiatric disorder, or chronic steroid intake. Pregnant/lactating women were excluded as well. Table 2 reports the distribution of sensitizations, and the average duration of treatments.

SLIT and concomitant drugs

All patients were prescribed a commercial SLIT treatment with a monomeric allergoid (8) in orosoluble tablets (LAIS, Lofarma S.p.A., Milan, Italy). The product was titrated in allergenic units (AU) and standardized according to the in-house reference preparation.

SLIT was performed for only one seasonal or perennial allergen, and it was administered over a period of about 3 years; the treatment course was continuous for mite allergy and preseasonal (in some cases continuous) for pollen allergy. The patients were carefully instructed by the prescribing physician concerning the modality of use of the SLIT and the dosage schedule. Moreover, the manufacturer provided clear written instructions. The buildup phase of about 8 weeks involved the administration, every other day, of increasing doses (25, 50, 100, 200, 300, 600, 1000, and 2000 AU) until the maintenance dose of 2000 AU was reached. This maintenance dose was then administered once a week. The tablets had to be taken in the morning, while the patient fasted, dissolved in the mouth for 1–2 min, and then swallowed (9).

All patients had to be well controlled by pharmacotherapy before starting SLIT, and they were prescribed an appropriate drug therapy to control their symptoms. The following drugs were used when indicated: oral antihistamines (cetirizine or loratadine), inhaled salbutamol, inhaled cromoglycate, low-dose inhaled corticosteroids (fluticasone propionate, budesonide, or beclomethasone dipropionate), and short courses of oral prednisone for severe rhinitis.

Follow-up for side-effects

The clinical assessment of safety was performed during the whole period(s) of SLIT, and all patients were regularly controlled at 3–4-month intervals, depending on their clinical situation. Patients were required to record on a proper diary card each dose administered and any local or systemic adverse event possibly related to SLIT administration. The side-effects were subdivided into eye symptoms, gastrointestinal complaints, rhinitis, asthma, urticaria, edema of tongue/lips, and anaphylaxis. Any other suspected adverse event possibly related to SLIT intake had to be described. The patients were also instructed to contact the centers when they needed medical advice. Therefore, according to the reports, the severity was graded as mild (no medical advice or treatment required, no interference with activities, no dose adjustment), moderate (interference with everyday activities and need for drug treatment and/or SLIT discontinuation), and severe (life-threatening events needing hospitalization and/or emergency care). The episodes of mild transient oral itching requiring neither dosage adjustment nor drug treatment were not considered relevant to the safety evaluation.

A subjective judgment of the effectiveness (based on symptoms and drug consumption) was asked of each patient. The treatment rankings were excellent (no drug therapy needed), good (only nasal or conjunctival antihistamines/cromoglycate used), moderate (minor reduction of drug intake, oral antihistamines and local steroids used), or insufficient (no reduction of drug intake).

Results

The average treatment period over 3 years ranged from about 9 months for pollinosis patients (usually treated preseasonally) to 32 months for patients allergic to mites. According to the schedule suggested by the manufacturer, about 32 800 doses were globally administered.

The side-effects reported are summarized in Table 3. Only 17 adverse events (three local) were reported, thus corresponding to 7.5% of patients and 0.52 per 1000 doses administered. Seven episodes of rhinitis (two in the same two patients), three of mild edema of lips, and one of abdominal pain were occasional and self-limiting: no drug therapy or schedule modification was needed. Two cases of urticaria and two of abdominal pain/nausea were optimally controlled by a temporary dose adjustment. In one case of urticaria and one of conjunctivitis, a single dose of oral antihistamine was sufficient to control symptoms. Therefore, medical intervention (dose adjustment or drug prescription) was required only in six patients over about 3 years. Rhinitis and conjunctivitis, occurred invariantly within 1 h, whereas abdominal pain had a variable onset. Surprisingly, 45 patients reported the onset of very mild somnolence 1–2 h after SLIT intake. No severe systemic side-effect was reported. The subjective judgment of the clinical effectiveness was excellent in 20%, good in 61%, moderate in 6%, and unsatisfactory in 13% of patients.

Discussion

The available DBPC trials suggest that SLIT is generally safe, but these studies usually involve small samples. Therefore, the need for an assessment in large populations has been claimed, and, of course, accurate description and quantification of side-effects are required. Frew et al. (6) correctly stated that "side-effects and adverse reactions need to be sought out, described and quantified so that . . . we can gain an accurate appraisal of the safety issues involved before we . . . recommend this form of immunotherapy for use in nonspecialist settings or at home."

In children, the only post-marketing surveillance so far conducted (5) reported a rate of 3% (0.083 per 1000 doses). In adults, a Spanish survey (3) reported

Table 1. Demographic data

	Number	% of total
Patients	198	100
Male	83	42
Female	115	58
Mean age (years)	24.4	–
Age range	15–51	–
Rhinitis	103	52
Asthma	21	10.5
Asthma and rhinitis	74	37.5

Table 2. SLIT treatments

Allergen	Patients	Total average duration (months)	Total number of doses administered
Dust mites	69	31.9	11 421
Grasses	75	9.2	12 136
Parietaria	46	16.3	7964
Birch	4	9.6	644
Olive	1	12.0	159
Compositae	3	12.0	439
Total	198	15.1	32 803

an overall rate of systemic side-effects of 0.77 per 1000 doses. Recently, André et al. (4) pooled and reviewed the results from eight DBPC trials performed in both adults (472 patients) and children (218 patients). A total of 145 adverse events were reported in the 343 subjects receiving SLIT, and 79 in the 347 receiving placebo. Only the side-effects involving the mouth (61 SLIT, 13 placebo) and the gastrointestinal tract (47 SLIT, 15 placebo) were significantly more frequent in the actively treated patients, whereas the occurrence of other side-effects was similar, and wheezing was more frequent in placebo patients. No difference between children and adults was found. Nevertheless, in all the DBPC studies, the survey of side-effects was a secondary outcome, and the classification and quantification of them were made arbitrarily and in a different way from study to study.

In this survey, the routine self-administration of SLIT was considered, and a standard questionnaire for side-effects was used. Therefore, these data represent a real estimate of the safety of the treatment in everyday practice, and they are not biased by the selection criteria used in the controlled clinical studies. The results from the present survey agree with the previous reports: the occurrence of side-effects was 7.5% of patients (corresponding to about one for every 2000 doses administered). It is noteworthy that about two-thirds (11/17) of the reported side-effects were of no clinical relevance, since they did not require either drug therapy or dose adjustment. The remaining side-effects were easily controlled and withdrawal of SLIT was never required. The safety of the product surveyed in this study was expected, since the monomeric allergoid is characterized by a substantial decrease of IgE-binding capacity; the absence of side-effects was reported by our group even in patients with oral allergy syndrome (10). The somnolence reported by 45 patients was a rather unexpected side-effect, and no pathogenic mechanism directly attributable to SLIT can be presently hypothesized. It has also to be considered that the majority of patients were also taking oral antihistamines, representing a confounding factor. The patients described their somnolence as very mild, and no interference with daily activities was reported. Nevertheless, this observation will require in the future a careful evaluation, possibly in comparison with placebo.

The self-administration of SLIT seemed not to represent a practical problem, although a careful and frequent follow-up of patients, as well as the constant availability of referral to a specialist, is recommended. SLIT appears to be safe in adult allergic patients, at least for the most common allergens. Indeed, no conclusive statement can be made about olive, birch, and Compositae, due to the small number of patients receiving SLIT for those allergens. In fact, in northern Italy, allergy to the mentioned pollens very rarely requires the prescription of immunotherapy.

Of course, more extensive surveys would be able to detect rare severe adverse events, if any. So far, we can conclude that, in the current clinical practice, the safety profile of SLIT is overall favorable.

Table 3. Characteristics of side-effects reported

Side-effect	Episodes	% of patients	Grade	Time of onset
Edema of lips	3	1.5	3 mild	<30 min
Gastrointestinal complaints	3	1.5	1 mild, 2 moderate	30–120 min
Rhinitis	7	2.5, 2 patients with 2 episodes	7 mild	<60 min
Conjunctivitis	1	0.5	1 moderate	45 min
Urticaria	3	1.5	3 moderate	>30, <60 min
Angiedema	0	–	–	–
Asthma	0	–	–	–
Anaphylaxis	0	–	–	–
Total	17	7.5	–	–

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