Short communication

Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients

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Background: Immunotherapy (IT) is the only causal treatment for allergic subjects recognized to be effective and to offer long-lasting efficacy. The noninjective routes, aimed at improving the safety of the treatment, have been validated as effective in adults, but documentation of their safety in children is still poor. The aim of the present survey study was to assess the safety of sublingual immunotherapy in pediatric patients, by evaluating a large population.

Methods: A total of 268 children (aged 2–15 years), receiving sublingual IT for respiratory allergy, were followed-up over a period ranging from 3 months to 7 years (mean 34 months). The side-effects possibly due to the treatment were recorded on a proper diary card; self-assessment of the clinical outcome was also evaluated.

Results: About 96 000 doses of extract were globally administered. Local side-effects were of no clinical relevance. Eight side-effects were reported (3% of patients; 0.083 per 1000 doses). Seven systemic side-effects (abdominal pain, conjunctival itching, and rhinitis) were mild and required no treatment. One case of urticaria was well controlled with oral antihistamines. No life-threatening event occurred. The clinical outcome was judged excellent or good by 80% of the patients.

Conclusions: The sublingual IT herein investigated appeared to be well tolerated and safe in pediatric patients. The risk/benefit ratio was therefore favorable.

Allergen-specific immunotherapy (IT) by the subcutaneous route was introduced into clinical practice at the beginning of this century. Such a long-lasting experience has allowed the accumulation of numerous data on clinical and

immunologic aspects of this kind of treatment. In particular, allergen standardization has been improved, the indications have been defined, and the preventive and long-lasting effects have been ascertained (1, 2). During the last 15 years, interest has increased, expecially in Europe, in local (or noninjective) routes of IT. The overall aim of these routes is to increase the safety and the compliance, which are of primary relevance especially to pediatric use and when the prophylactic rationale is considered. On the available experimental data, the WHO (3) and the EAACI/ESPACI (4) have accepted nasal and sublingual IT as viable alternatives to injection IT. Many controlled trials support the efficacy and safety of sublingual (5–14) IT in adults, whereas the pediatric experience is still judged to be poor (15, 16), and further trials are recommended (3, 4). The main concern about the use of local IT in children is, of course, the safety aspect, which can be elucidated only by surveying a large number of patients.

We planned a long-term survey on more than 200 children receiving sublingual IT for respiratory allergy, in order to evaluate the clinical safety of the treatment and possibly to detect low-incidence side-effects that are not seen in clinical trials.

Material and methods

Patients

A total of 268 children (aged 2–15 years) receiving sublingual IT for respiratory allergies were followed up. IT was prescribed after a careful evaluation of clinical history, causal role of the allergen(s), and cost/benefit ratio. In detail, skin test and/or RAST positivity (class 3 at least), clinical history of rhinitis and/or asthma, and capacity to comply with the treatment were required. None of the patients had previously received IT, and none of them had contra-indications. The demographic characteristics of the patients are summarized in Table 1, Table 2 reports the distribution of sensitizations, and Table 3 summarizes the prescribed IT and the average period of treatment. Most patients (53.7%) were treated only with mite allergens, while grasses and Parietaria extracts were used to a lesser extent (25.4% and 5.6%, respectively); only two patients (0.75%) received IT for Alternaria. About 15% of the patients received IT for two allergens as separate treatments.

Table 1. Patient population

	Number	% of total
Patients	268	
Male	173	64.55
Female	95	35.45
Mean age (years)	7.7	
Age range	2–15	
Rhinoconjunctivitis	102	38.06
Asthma and rhinoconjunctivitis	100	37.31
Asthma	66	24.63

Sublingual IT and concomitant therapy

Sublingual IT was performed in all patients by commercial preparations (ALK-Abellò, Milan, Italy) of biologically standardized vaccines (17, 18) in glycerinated (50% v/v) physiologic solution, preserved with phenol 0.4% (w/v). The schedule involved daily administration of increasing doses of the extract, followed by a maintenance top dose given three times a week, according to the manufacturer's instructions. In patients sensitized to perennial allergen, IT was administered during the whole year without interruptions or dose variations. In patients allergic to pollens, a pre-coseasonal administration was performed, starting 2–3 months before the beginning of the pollen season, and the maintenance dose reduced by 60% was administered twice weekly until the end of the pollination period. All patients had to be well controlled by pharmacotherapy, if any, when beginning IT treatment. IT was performed only for one or at most two (non-cross-reacting) seasonal allergens, whereas IT for mites was always administered alone. In patients sensitized to both seasonal and perennial allergens, a single allergen was chosen for IT, based on clinical history.

Table 2. Sensitizations (skin test and RAST $\geq$ class 3)

Allergen	% Sensitized patients
Dust mites	70.9
Grasses	54.5
Parietaria (pellitory)	16.1
Molds	6
Olive	4.1
Cat	1.9
Single sensitization	54.9
Two allergens	34.3
More than two allergens	10.8

Table 3. Characteristics of prescribed IT treatments

	No. of patients	% of population	Average treatment duration (months)
Dust mites	144	53.7	32.3
Grasses	68	25.4	34.6
Parietaria	15	5.6	35.5
Alternaria	2	0.75	33
Multiple sensitization	39	14.6	36

All patients received proper pharmacotherapy in order to control their symptoms. The following drugs were used when indicated: inhaled cromolyn, nasal steroids, inhaled albuterol, oral antihistamines (cetirizine or loratadine), and oral corticosteroids (betamethasone or deflazacort).

Follow-up for side-effects

All patients' parents were carefully instructed in the use and self-management of IT, and all patients were regularly seen at 4-month intervals. They were required to record on a proper diary card each dose administered and any local or systemic adverse event possibly related to IT administration. For convenience, the possible side-effects were subdivided into eye symptoms, gastrointestinal complaints, rhinitis, asthma, urticaria, and angioedema. Obviously, any other kind of suspected adverse event had to be described. The severity was classed as either low (no need for treatment and no interference with everyday activities), moderate (interference with everyday activities and need for drug treatment), or severe (life-threatening events needing hospitalization and/or emergency care). Short-lasting and self-resolving local effects (namely, oral itching), requiring neither dosage adjustment nor treatment were not considered.

A subjective evaluation of the clinical outcome (based on symptoms and drug consumption) was also required. The treatment was judged to be excellent if no drug therapy was needed, good if only local (inhaled/nasal/conjunctival) therapy was used without steroids, and moderate or insufficient if there was only a minor or, respectively, no reduction of the drug intake.

Results

The average treatment period in the patients' population was around 34 months, irrespective of the allergen used. According to the suggested schedules, about 96 000 doses were administered. The side-effects reported are summarized in Table 4. Only eight adverse events were recorded, thus corresponding to 3% of patients and one per 12 000 administrations. In seven cases, no drug therapy was required, but only a dosage adjustment; in one case of urticaria, a single dose of oral antihistamine was sufficient to control symptoms. In one patient, abdominal pain (self-resolved within 2 h) occurred because of a dose error. It was noteworthy that rhinitis was the only early (within 30 min) side-effect reported. Oral itching occurred in around 7% of patients; it was always short-lasting and never required drug therapy or dosage adjustment.

The subjective judgment of the clinical effectiveness was as follows: excellent in 29% of patients, good in 51%, and moderate or insufficient in 20%.

Discussion

Our knowledge of the safety of sublingual IT derives from the controlled studies performed in adults (5–14) and children (15, 16), and from a Spanish post-marketing surveillance study (19). In adults, the occurrence of side-effects was reported to range between 0 (6, 13, 14) and 7 per 1000 administrations (12). The Spanish survey in young adults reported an occurrence of systemic side-effects of 0.77 per 1000 doses administered. Few data are available for

Table 4. Characteristics of reported side-effects

Side-effect reported	Episodes	% of patients	Grade	Onset
Conjunctival itching	1	0.37	Mild	>30 min
Abdominal pain (*)	1	0.37	Mild	>30 min
Rhinitis	5	1.9	Mild	<30 min
Urticaria	1	0.37	Moderate	>30 min
Total	8	3		

*Wrong (high) dose administered.

pediatric patients: the reported rate of side-effects ranged between 0% and 3.73 per 1000 doses (15, 20).

In the present study, conducted in a large pediatric population, we found an overall rate of side-effects of 3% of patients (corresponding to about 0.083 per 1000 doses administered). The doses of allergens used herein are identical to those used in similar double-blind, placebo-controlled or open studies to show the efficacy of the drug manufactured by the same producer (5, 6, 8, 11, 14, 20). Rhinitis was the only early side-effect, while the others appeared more than 30 min after administration. It is noteworthy that no life-threatening side-effect was reported in the present survey, in agreement with the literature of the past 15 years, and the incidence of side-effects appeared to be lower than that reported for injective immunotherapy. Furthermore, the clinical outcome of the IT treatment was judged to be satisfactory by the majority (around 80%) of the patients and the self-management of sublingual IT did not seem to represent per se a problem. In any case, careful and frequent follow-up of patients is recommended by the international guidelines.

In conclusion, the data herein reported confirm that sublingual IT is safe in pediatric patients and that the risk/benefit ratio is favorable.

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