

Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years

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Summary

Background The age below 5 years is considered a prudential limit for immunotherapy in view of the possible severity of side-effects. Sublingual immunotherapy (SLIT) seems to be safe, but no study in very young children is available. We performed a safety post-marketing surveillance study in children below 5 years.

Methods Children aged 3–5 years with respiratory allergy receiving SLIT were followed-up for at least 2 years. A diary card for side-effects was filled by parents at each dose given. Local and systemic side-effects were graded as: mild (no intervention, no dose adjustment), moderate (medical treatment and/or dose reduction), severe (life-threatening/hospitalization/emergency care). The comparative safety of different allergens and regimens was also assessed.

Results One hundred and twenty-six children (mean age 4.2 years, 67 male) were included. Seventy-six (60%) had rhinitis with asthma, 34 (27%) rhinitis only and 16 (13%) only asthma. Immunotherapy was prescribed for mites (62%), grasses (22.2%), *Parietaria* (11.9%), *Alternaria* (2.4%) and olive (1.5%). Eighteen children underwent an accelerated build-up. The total number of doses was about 39 000. Nine side-effects were reported in seven children (5.6% patients and 0.2/1000 doses). Two episodes of oral itching and one of abdominal pain were mild. Six gastrointestinal side-effects were controlled by reducing the dose. All side-effects occurred during up-dosing phase. No difference in terms of safety among the allergens used was observed.

Conclusion SLIT is safe also in children under the age of 5 years.

Keywords children, respiratory allergy, safety, side-effects, sublingual immunotherapy

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Introduction

Sublingual immunotherapy (SLIT) is used in many European countries since at least 10 years, and it has been approved in clinical practice in the recent official documents [1, 2]. In fact, the efficacy of SLIT is supported by a large number of randomized controlled trials [3], and a recent meta-analysis study has provided confirmatory data, at least in allergic rhinitis [4]. In addition to efficacy data, three post-marketing surveillance studies [5–7], one of them also including some very young patients [5], have shown that SLIT has a very low incidence of side-effects. In a direct comparison, a safety profile even more favourable than subcutaneous immunotherapy (SCIT) was shown [8]. The safety itself seems to be the major advantage of SLIT, and this may be of special relevance in paediatric age, where a greater benefit of immunotherapy is expected. With SCIT, the age below 5 years is considered as a relative contraindication [1], because

it is known that severe side-effects are more difficult to treat in very young children. In addition, the risk of severe adverse events of injections in children is low, but not negligible.

With SLIT, neither life-threatening systemic events nor fatalities has ever been reported over more than 15 years of clinical use and controlled trials, and the occurrence of side-effects seems not to differ between adults and children [9]. This is true, independent of the administration regimen, because also accelerated build-up schedules are well tolerated [10, 11]. As a general impression from the everyday clinical practice, SLIT seems to be well tolerated also in very young children, and the age below 5 years seems not to increase the risk of adverse events. Nevertheless, so far there is no quantitative assessment of this fact, and the safety in young children still remains to be demonstrated. In addition, the fact that SLIT is administered at home and has to be directly managed by parents represents a concern from the point of view of the safety that needs a reliable answer.

For this reason, we undertook a 2-year multi-centre prospective post-marketing surveillance to assess the safety profile of SLIT in drops, in children aged 3–5 years. The study was conducted with a commercial preparation of SLIT, with different allergens and different administration schedules.

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Material and methods

General plan

This was a prospective post-marketing surveillance, conducted in four different Italian centres, involving children of 3–5 years of age. The follow-up period was of 2 years $\pm$ 1 month. SLIT was prescribed only after a detailed diagnosis of respiratory allergy was made and the parents of the children were carefully instructed on how to administer the SLIT and how to manage the side-effects. A paediatric allergist was always available at each centre for phone advice. During the SLIT courses, parents were asked to carefully fill a specific diary card, recording any side-effect possibly related to SLIT administration. Skin test and RAST assay were performed at baseline and after 2 years of SLIT treatment. The study was approved by the Ethical Committees, and all parents signed an informed consent.

Patients and diagnosis

Children with an age between 3 and 5 years were included in this survey. They had to suffer from allergic asthma and/or rhinoconjunctivitis. The IgE-mediated aetiology was confirmed by skin prick test and RAST assay positivity. The diagnosis of rhinitis and/or asthma was essentially clinical, because the very young age of children did not allow performing instrumental measurements (e.g. spirometry). Because of the age, we could not exclude episodes of asthma and/or wheezing caused by viral respiratory infections, but a doctor-diagnosed episode of wheezing/difficult breathing or rhinitis, without evidence of upper/lower respiratory infections, on at least three occasions was required. Moreover, children allergic to pollens had to display a clear seasonality (i.e. exposure related symptoms). All children had to suffer from their disease from at least 12 months. Skin prick tests were performed in all children with a standard panel of commercial extracts for the relevant allergens, including: house dust mites, grasses, *Parietaria*, olive, birch, cat dander, dog dander, *Alternaria tenuis*, *Cladosporium herbarum* and mugwort. Skin testing was performed according to international guidelines. RAST assays were performed using the CAP-system (Pharmacia, Uppsala, Sweden) for the same allergens used in the prick tests. A class 3 or higher was required for positivity.

Immunotherapy

SLIT was given as commercial product (ALK-Abellò, Lainate, Milan, Italy), in drops (aqueous glycerinated 50% solution, phenol 0.4%) to be kept under the tongue for 1–2 min then swallowed. It was administered in the morning (and also in the afternoon with the accelerated build-up), being the patient fasted. The extracts used were biologically standardized in standard treatment units (STU) and prepared in four different 5 mL vials at increasing concentrations: 1.6, 8, 40, 200 and 1000 STU/mL. For most of the extracts, the content of the major allergen(s) was also expressed in micrograms (see below). Two build-up regimens were used: (a) the traditional up-dosing schedule with one dose per day, lasting 30 days; (b) an accelerated schedule, lasting 15 days, with a twice daily administration (morning and in the

afternoon). During the maintenance phase, five to seven drops from the highest concentration vial were given three times a week.

SLIT was given for a single clinically relevant allergen, but in a minority of patients two extracts had to be used. For mites and *Alternaria*, the maintenance dose was given continuously, whereas for pollens the administration was pre-coseasonal (January to June for grasses and olive, December to July for *Parietaria*), with a reduction of the dose to three drops three times a week during the pollen season.

All children received an appropriate therapy for symptomatic control, which was adjusted case by case throughout the study period. Drug therapy included: nasal/inhaled cromolyn, inhaled salbutamol on demand, inhaled fluticasone or beclometasone, oral cetirizine and oral montelukast.

Side-effects

A diary card for side-effects was given to the parents, asking to carefully fill it at each dose given. Side-effects were subdivided into: eye symptoms, rhinitis, asthma, oral itching, gastrointestinal complaints (nausea, vomiting, abdominal pain, diarrhea), urticaria, angioedema, and anaphylaxis. They were graded as mild (no need for treatment or dose adjusting), moderate (need for drugs/medical advice or dose adjusting or SLIT discontinuation), and severe (life-threatening or hospitalization or emergency care needed) [5].

Results

One hundred and twenty-six children were included in this survey, and all completed the 2-year observation period. Their mean age was 4.2 years (range 3–5), and 67 of them were male. Seventy-six (60%) children had rhinitis with asthma, 34 (27%) had rhinitis only and 16 (13%) had only asthma.

Eight children received SLIT for two allergens, with a mixture prepared by the manufacturer. The prescribed SLIT and the demographic characteristics of the children are summarized in Table 1. The traditional build-up phase was used in 108 patients, whereas 18 (10 mites, 6 grass, 2 olive) received an abbreviated up-dosing schedule. Table 2 summarizes the doses of allergen given with the various regimens of SLIT. For mites, *Parietaria* and *Alternaria* the difference in the cumulative dose is because of the maximum maintenance dose that was either five drops or seven drops three times a week, depending upon the preference and personal experience of physicians. The total number of doses given in 2 years was about 39 000 (Table 2). The cumulative dose for a given period was 3.25–7 times (depending on the allergen) greater than the equivalent SCIT dose from the same manufacturer.

In total, nine side-effects were reported in seven patients, corresponding to 5.6% of patients and about 0.2 per 1000 doses administered. The characteristics of the side-effects are summarized in Table 3. Two of the episodes were local (oral itching): they were mild and transient and did require neither dose adjustment nor medical intervention. Seven side-effects were systemic and involved the gastrointestinal tract. In one child, abdominal pain was mild, and self resolved without

Table 1. Demographic data of the patients' population

SLIT administered	n (%)	Sex (M/F)	Mean age (range) (years)	Single sensitization	Disease*
House dust mite (three mix dust mite + <i>Alternaria</i>)	78 (62)	36/42	4.16 (3–5)	54	13 R, 14 A, 51 R+A
Grasses (four mix Grass+olive, one mix grass + <i>Alternaria</i>)	28 (22.2)	17/11	4.14 (3–5)	16	10 R, 18 R+A
Olive	2 (1.5)	1/1	4.5 (4–5)	1	1 R 1 R+A
<i>Parietaria</i>	15 (11.9)	11/4	4.6 (3–5)	6	9 R, 2 A, 4 R+A
<i>Alternaria</i>	3 (2.4)	2/1	4.3 (4–5)	2	1 R, 2 R+A
Total	126	67/59	4.2 (3–5)	79	34 R, 16 A, 76 R+A

*R, rhinitis; A, asthma.

SLIT, sublingual immunotherapy; M, male; F, female.

Table 2. Allergen dosages

Treatment	N	Allergen	Maximum maintenance dose (µg)	Cumulative dose per year (µg) (maintenance)	Number of doses in 2 years
Dermatophagoides mix	38	Der 1	1.12	174.72	25 650
		Der 2	0.56	87.36	
Dermatophagoides mix	35	Der 1	0.80	124.80	6,936
		Der 2	0.40	62.40	
Dermatophagoides pteronyssinus	2	Der p1	0.80	124.80	990
		Der p2	0.40	62.40	
Dermatophagoides mix (70%) + <i>Alternaria</i> (30%)	2	Der 1	0.56	87.36	380
		Der 2	0.28	43.68	
		Alt a 1	0.02	2.81	5,076
Dermatophagoides mix (60%) + <i>Alternaria</i> (40%)	1	Der 1	0.48	74.88	
		Der 2	0.24	37.44	990
		Alt a 1	0.02	3.74	
Grass mix	23	Group 5	0.70	39.30	380
Grass mix (50%) + olive (50%)	2	Group 5	0.35	19.65	
		Ole e 1	2.10	117.90	990
Grass mix (80%) + olive (20%)	2	Group 5	0.56	31.44	
		Ole e 1	0.84	47.16	380
Grass mix (80%) + <i>Alternaria</i> (20%)	1	Group 5	0.35	31.44	
		Alt a1	0.02	0.94	5,076
Olive	2	Ole e 1	3.00	195.00	
<i>Parietaria judaica</i>	9	Par j 1	0.17	23.86	990
<i>Parietaria judaica</i>	6	Par j 1	0.12	18.72	
<i>Alternaria</i>	2	Alt a 1	0.08	13.10	380
<i>Alternaria</i>	1	Alt a 1	0.06	9.36	
TOTAL	126				39 032

Table 3. Description of the side-effects

Patient	Sex	Age (years)	Side-effect	Allergen	Grade	Onset time	Rush build-up	Action taken
1	M	3	Oral itching	Mite	Mild	< 30'	Yes	None
2	M	4	Oral itching	Mite	Mild	< 45'	No	None
3	F	4	Abdominal pain	Mite	Moderate	< 45'	No	None
4	F	5	Diarrhoea	<i>Parietaria</i>	Moderate	2.5 h	No	Spit
5	F	5	Abdominal pain and diarrhoea	Mite	Moderate	1.5 h	No	Spit
6	M	4	Diarrhoea	Grass	Moderate	2 h	Yes	Spit
7	M	4	Abdominal pain and diarrhoea	Grass	Moderate	1.5 h	No	Spit

M, male; F, female.

medical intervention or dosage adjusting. In the remaining six cases abdominal pain was accompanied by diarrhoea. In those cases, it was suggested to spit the allergen after keeping it in the mouth (SLIT-spit), and problems completely

disappeared, without discontinuing the treatment. All the side-effects occurred during up-dosing phase. The local untoward effects appeared rapidly (<45 min), whereas abdominal pain and diarrhoea had variable onset time.

Concerning the allergen, the side-effects occurred in 4/78 (5.1%) of children receiving mites, in 2/28 (7%) with grass SLIT and 1/15 (6.5%) with *Parietaria*. Therefore, no difference could be detected in terms of safety among the different allergenic extracts. Moderate side-effects occurred in 1/18 (5.5%) patients with the accelerated build-up and in 4/108 (3.7%) with the traditional up-dosing, thus no significant difference seemed to exist between the two regimens. Finally, there was no appreciable difference in side-effects' occurrence among the centres involved. New skin sensitizations with respect to the baseline pattern appeared in eight previously monosensitized children, whereas in six children there was a reduction in the number of skin positivities. In the remaining children, skin sensitizations remained unchanged.

Discussion

SLIT is now approved for clinical use in the recent official documents [1, 2] and it is widely prescribed in several European countries. Some concerns still exist about the use and indications of SLIT in children, although the few paediatric clinical studies conducted so far [12–16] are encouraging. It is reasonably expected that immunotherapy in general can have a better outcome if given at the early stages of the disease, and it has been recently demonstrated that SLIT can prevent the onset of asthma [17] in children, identically to SCIT [18]. In addition, it was noticed with SLIT that the magnitude of the clinical efficacy is greater in younger patients [19]. Indeed, with SCIT, the age below 5 years is considered as a relative contraindication [1], because severe side-effects are more difficult to treat in very young children, and injection immunotherapy carries the risk, even if low, of important untoward reactions [20]. It is also true that the conventional limit of 5 years is dictated mainly by prudential consideration, but it is accepted that, under strict control, the treatment can be given also to younger children. SLIT is a good candidate for the management of respiratory allergy in very young children, based on its favourable safety profile [5–7]. In this regard, it seems reasonable to obtain reliable data on the safety before planning double-blind controlled studies to evaluate the efficacy in this age range.

Indeed, in clinical practice SLIT is sometimes prescribed by paediatricians in children below 5 years of age also, and it seems to be well tolerated. In the previous post-marketing surveillance study the 13 (out of 268) patients below 5 years tolerated well the treatment. In another recent report, it was shown that the occurrence of side-effects in children 2–5-year-old was low, but that preliminary survey involved only 36 patients [21]. These results were encouraging, but the samples were small, thus rare side-effects could not be detected. We planned the present survey in order to span a large population of young children, and in order to verify whether the safety profile remains satisfactory even in a real life setting, where SLIT is used in everyday clinical practice. One hundred and twenty-six children were followed-up for 2 years, with a diary card for side-effects to be filled by parents at each dose. All the parents carefully followed the instructions and no patient was lost to follow-up. The occurrence of side-effects did not differ from that reported in previous surveys [5, 7], being the

rate per patient about 7%. All side-effects involved the gastrointestinal tract, as reported in clinical trials [22], and could invariably be controlled with a reduction of the dose, without discontinuing the treatment. This is in accordance to what was observed with oral immunotherapy [23] and with SLIT with very high doses [12]. For simplicity purpose, the sublingual-spit modality was used to manage side-effects. Based on pharmacokinetics studies this corresponds to a reduction of 30%–50% of the dose given [24]. On the other hand, the sublingual/spit modality seems to have the same occurrence of side-effects [7]. All adverse events appeared during the induction phase, independent of the use of a traditional or accelerated schedule. This fact suggests that, with SLIT, a slow build-up is not necessary [10, 25]. Finally, it is unlikely that the low incidence of side-effects is because of a too low amount of allergen. The same extract at the same dosage was previously proven effective with *Parietaria* [11, 26, 27] and grasses [17]. For olive, the dose was even higher than that used in another study with another extract [13]. Also with mites, two studies reported clinical efficacy [16] and long-lasting effect [28] in children, with a cumulative yearly dose comparable with that used in the present protocol. Concerning *Alternaria* there is a single efficacy study [29], where higher doses were used. It is true that the doses used in clinical trials are largely variable, and our results on the safety should be limited to the specific SLIT protocols used. On the other hand, the present data are in agreement with those from other post-marketing surveys [6, 7, 21].

Our data, obtained in a real-life setting confirm that SLIT at the indicated doses is safe below the age of 5 years. This finding can be regarded as preliminary to plan clinical trials, aimed at rigorously measuring the clinical effects (including prevention) of these SLIT protocols. In addition, the demonstration of safety is confirmatory to the already ongoing use in clinical practice. In this sense, it is important to remember, however, that in very young children a detailed diagnosis of IgE-mediated allergy, made by a specialist is mandatory to justify the risk/benefit ratio.

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