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Short communication

The safety of sublingual immunotherapy with one or multiple pollen allergens in children

Background: Since the majority of allergic patients are polysensitized, it is often necessary to prescribe immunotherapy with multiple allergens. It is crucial to know if the administration of multiple allergens with sublingual immunotherapy (SLIT) increases the risk of side-effects in children.
Methods: Consecutive children with respiratory allergy because of pollens, receiving SLIT for multiple or single allergens were followed-up in a postmarketing survey. Inclusion criteria were those for prescribing SLIT according to guidelines. Parents recorded in a diary card the side-effects (eye symptoms, rhinitis/ear itching, asthma, oral itching/swelling, nausea, vomiting, abdominal pain, diarrhoea, urticaria, angioedema and anaphylaxis). The side-effects were graded as mild, moderate and severe.
Results: Four hundred and thirty-three children (285 male, age range 3–18 years) receiving SLIT were surveyed. Of them, 179 received a single extract, and 254 multiple allergens. The total number of doses given was 40 169 (17 143 with single allergen). Overall, 178 episodes were reported. Of them, 76 occurred with the single allergen (42.46% patients, 4.43/1000 doses) and 102 (40.3% patients, 4.42/1000 doses) with multiple allergens (P = NS). 165 episodes (92.5%) were mild and self-resolving and were equally distributed in the two groups. In 13 cases, the events were judged of moderate severity and medical advice was required. Three patients discontinued SLIT, despite the local side-effects being mild. No emergency treatment was required at all.
Conclusion: The use of multiple allergens for SLIT does not increase the rate of side-effects in children.

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Sublingual immunotherapy (SLIT) is now recognized as a viable alternative to the classical injection route (1, 2) and it is currently used in everyday clinical practice in several European Countries. In addition to the well-demonstrated clinical efficacy (3), one of the distinguishing features of SLIT is its good safety profile, which has been repeatedly confirmed in both clinical trials (4) and postmarketing surveys (5–7). In this regard, it is well recognized from the literature that systemic and/or severe side-effects are exceptional, and these side-effects usually do not differ between placebo and treated groups (8). Nonetheless, it is true that all clinical trials were performed with a single allergen extract and so was performed in the postmarketing surveys. This is because of the fact that, at least in Europe, there is the tendency to prescribe immunotherapy for one allergen, which is recognized as the responsible for the disease (9). On the contrary, the vast majority of patients are polysensitized (10) and different allergens can cause their symptoms, so that a vaccination with multiple allergens is often required and justified. Of note, the administration of multiple allergens is a common practice in the USA and other countries (11).

Very recently, concerns of the safety of SLIT when different allergens are given together have been raised, based on isolated case reports (12, 13). Certainly, this aspect becomes one of primary relevance in children who are, in principle, the ideal candidates to SLIT, especially based on safety considerations. In other words, it is essential to know if in children the administration of more than one allergen may increase the occurrence of adverse events. For this reason, we compared in a postmarketing survey, by means of proper diary cards, the rate of side-effects in paediatric patients receiving SLIT either with single or multiple allergens.

Methods

Consecutive paediatric patients with respiratory allergy due to pollens, seen in the period 2004–2007 receiving SLIT for multiple allergens and matched patients treated with one single allergen were followed-up in this postmarketing survey. Inclusion criteria were those for prescribing SLIT according to guidelines (2). In particular, SLIT was given to those children suffering from respiratory allergy

(rhinitis and/or asthma), when the causal role of the allergen(s) was well ascertained based on clinical history, exposure timing and sensitization assessed by skin prick tests and/or CAP-RAST assay. In selected cases, specific nasal or conjunctival challenges were performed to better identify the causal allergens. Allergic rhinitis and asthma were diagnosed according to current guidelines recommendations (2, 14). Once SLIT was prescribed, the patients were followed-up during the immunotherapy courses by means of diary cards, where parents were carefully instructed to report and grade all the possible side-effects mentioned in the diary even if negligible (6). Commercial extracts from three manufacturers (ALK-Abellò, Italy, Lainate, Milan, Italy; Lofarma S. p. A., Milan, Italy; Stallergenes, Antony Cedex, France), equally distributed among patients were used at the recommended doses. The build-up lasted 6 days with the Lofarma extracts, and 9 days with the Stallergenes and ALK-Abellò products. In the diary card, the side-effects were subdivided into: eye symptoms, rhinitis/ear itching, asthma (including cough, shortness of breath, wheezing and chest tightness), oral itching/swelling, gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea), urticaria, angioedema and anaphylaxis. The side-effects were graded as mild (no treatment or dose adjusting), moderate (need for drugs/medical advice or dose adjusting), and severe (life-threatening/hospitalization/emergency care). A section of the diary was left available for the open description of any other untoward event, if any. All patients received the first dose of SLIT at the clinic, and a designated physician was always available for phone contact. In addition to SLIT, all patients were prescribed the appropriate pharmacological treatments for their diseases. Clinical visits were scheduled at variable time intervals, but not exceeding 3 months. On these occasions, diary cards were reviewed and collected.

Table 1. Prescribed SLIT

Single allergen *n* (%)		Multiple allergens *n* (%)	
Grass	161 (89.9) 36 precoseasonal	Grass + Trees	228 (90) 64 precoseasonal
Birch	14 (7.9) 4 precoseasonal	Grass + Olive	18 (7) 6 precoseasonal
Parietaria	4 (2.2)	Grass + Parietaria	6 (2.6)
		Grass + Mugwort	1 (0.2)
		Trees mix*	1 (0.2) precoseasonal
Total	179		254

*Hazelnut + alder + birch

Table 2. Summary of the reported side-effects

	Single allergen 179 patients, 17 143 doses	Multiple allergens 254 patients, 23 026 doses
Oral itching/burning	37 Mild, 4 moderate	48 Mild, 5 moderate
Oral/tongue swelling	9 Mild	11 Mild, 1 moderate
Rhinitis/ear itching	3 Mild	2 Mild
Throat irritation	14 Mild, 1 moderate	22 Mild, 2 moderate
Nausea/abdominal pain	3 Mild	4 Mild
Vomiting/diarrhoea	–	–
Cough	5 Mild	7 Mild
Asthma	–	–
Generalized urticaria	–	–
Anaphylaxis	–	–
Total	76 Episodes 42.46% Patients 4.43/1000 Doses	102 Episodes 40.32% Patients 4.42/1000 Doses

Results

Four hundred and thirty-three children (285 male, age range 3–18 years) receiving SLIT were surveyed. Of them, 179 (121 male, 101 with rhinoconjunctivitis and asthma) were treated with a single allergenic extract, and 254 (165 male, 175 with rhinoconjunctivitis and asthma) received multiple allergens. The treatments were continuous in 322 subjects and precoseasonal in 111. The total number of doses given was 40 169 (17 143 with a single allergen and 23 026 with multiple allergens). The duration of the follow-up ranged from 6 to 24 months, according to the duration of the prescribed treatment. Because of the characteristic of the geographical region, grass was the most prescribed extract, as it accounted for 89.9% of the single allergen prescriptions and was always present in the multiple treatments (Table 1).

As shown in Table 2, overall, 178 episodes were reported during the follow-up. Of them, 76 occurred with the single allergen and 102 with multiple allergens, and thus no difference in all and each side-effect rate was detectable between groups (Chi square = NS). Of note, 165 episodes (92.6%) were mild and self-resolving and were equally distributed in the two groups. Identically, 93.5% of the adverse events were described as local (Table 2). Ninety-five percent of the adverse events occurred during the induction phase, and always within 30 min from the administration. No particular increase of side-effects could be seen when new batches were started. In 13 cases, the events were judged of moderate severity and a temporary dose reduction was successfully applied. None of the patients required emergency treatments with bronchodilators or adrenaline. According to parents' requirement, SLIT was discontinued in three children (two with multiple allergens) for the persistence of oral itching. Because of the small number of adverse events, no difference among the three manufacturers could be seen.

Discussion

The problem of the safety of SLIT with multiple allergens has been underlined by two recent case reports of anaphylaxis (12, 13). Indeed, in those cases, more than five different allergens were mixed together, and this is definitely not the common way to use immunotherapy in Europe. In one case (12), the diagnosis was questioned (15) as the diagnostic criteria were not fulfilled, whereas in the other case nonstandardized extracts in an extemporaneous mixture were used (13). Apart from these case reports, the safety of SLIT with multiple allergens has to be substantiated, especially in children. In this postmarketing survey, we compared in a real-life setting the rate

of side-effects in paediatric patients receiving SLIT for either one or multiple pollen allergens. We could not find any difference in the occurrence of side-effects according to the number of allergens used, being the mild local side-effects being the more frequent ones. This is in agreement with the results of a previous report (16) in more than 150 adult patients, where the rate of side-effects was 55% of patients and 6.6/1000 doses with a single allergen and 56% and 6.3/1000 doses with multiple allergens, respectively. Of note, the rate of adverse events per patient was quite higher than in a previously published postmarketing survey (6). Indeed, the same instrument was used, but in the present protocol, patients were carefully instructed in events report (even if negligible or not troublesome at all), giving an expected slight increase of total events.

The overall number of patients is relatively small, but the reliability of the data is supported by the concordance of the figures with those reported in larger samples (3–5). The administration of multiple allergens leaves open the problem of the efficacy of mixtures, for which there is currently a single study available (17), and of the possible degradation of mixed extracts when proteases are present. On this latter aspect, no datum is available for SLIT.

Our conclusion is that SLIT with a limited number of mixed allergens does not increase the risk of side-effects in children. This does not exclude that the treatment must be correctly prescribed, standardized extracts are used and patients are carefully instructed on how to manage the treatment.

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