The safety of sublingual immunotherapy with one or more allergens in adults

C. Lombardi, S. Gargioni, M. Cottini, G. W. Canonica, G. Passalacqua*

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Sublingual immunotherapy (SLIT) is currently largely prescribed and used in many European countries, and its favourable safety profile is well ascertained. In this regard, it is well recognized from the literature that systemic and/or severe side-effects are exceptional. Nonetheless, it should be kept in mind that in Europe, SLIT is usually prescribed for a single allergen that is recognized as the principal responsible for symptoms. On the other hand, on the basis of results of the diagnostic workup, it is sometimes necessary to give SLIT for more than one allergen, when multiple allergens are clearly recognized to be the causal agents. Recently, two reports described the occurrence of anaphylaxis following the administration of multiple allergens (1, 2), thus raising concerns on the safety of multiple extracts given at the same time. For this reason, we compared the occurrence of side-effects in patients receiving SLIT with a single or multiple allergens.

A post-marketing survey on the safety of sublingual immunotherapy.

Consecutive patients suffering from respiratory allergy caused by pollens (rhinitis and/or asthma) eligible for specific immunotherapy with multiple allergens, and matched patients receiving SLIT for a single allergen were followed-up by means of diary cards for the identification of side-effects (3). Sublingual immunotherapy was prescribed according to guidelines, and multiple allergens were given only when the causal role of the allergens themselves was well ascertained. The SLIT was prepared as glycerinated solution containing either one single or multiple allergens, according to the prescription. The vaccination course involved a 10-day build-up phase with a daily increasing number of drops, followed by a maintenance phase where a single-dose vial was given daily for 3 months (SLIT-One; ALK-Abellò, Linate, Italy). All patients received the first dose of SLIT at the clinic, and were then instructed to fill a diary card for adverse events. Side-effects were subdivided into: eye symptoms, rhinitis/ear itching, asthma, oral itching/swelling, gastrointestinal (nausea, vomiting, abdominal pain, diarrhea), urticaria, angioedema, and anaphylaxis. They 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).

One hundred and fifty-nine patients received SLIT either for a single allergen (n = 76, 36 male, age range 16–59 years, 27 rhinitis only) or multiple allergens (n = 83, 40 male, age range 19–57 years, 30 rhinitis only) for a total of 15 347 doses. The prescribed SLITs are summarized in Table 1. There were 45 episodes in 42 patients of the first group and 51 episodes in 47 patients of the other group; thus the rate of side-effects did not differ between the groups (χ^2 = NS). The reported 96 events were mainly local and appeared always in the induction phase (Table 2). Almost all the events were mild, self-limiting and required no medical intervention, but two episodes of oral angioedema, for which medical advice was required. These were judged as moderate, and successfully treated with oral antihistamines and a temporary interruption of the dose escalation. None of the patients had to stop the SLIT course and no emergency treatment with bronchodilators or adrenaline was required at all.

In the present postmarketing survey, we compared in a real-life setting the rate of side-effects in patients receiving SLIT for either one or two allergens. This exploratory survey was prompted by the

Table 1. Prescribed sublingual immunotherapy

Single allergen n (%)		Multi allergens n (%)	
Grass	38 (50)	Grass + parietaria	31 (37.5)
Parietaria	20 (26.3)	Grass + birch	21 (25)
Birch	15 (19.7)	Grass + birch + alder + hazelnut	20 (24.5)
Ragweed	2 (2.6)	Grass + olive	1 (1.2)
Olive	1 (1.3)	Grass + mugwort	1 (1.2)
		Birch + hazelnut + alder	9 (10.6)
Total	76 (100)		83 (100)

Table 2. Characteristics of the reported side-effects

	Single allergen 76 patients, 7296 doses	Multiple-allergens 83 patients, 8051 doses
Side-effects (episodes)		
Oral itching/swelling	25 mild	27 mild
Oral angioedema	1 moderate	1 moderate
Rhinitis/ear itching	3 mild	4 mild
Throat irritation	5 mild	7 mild
Cough	6 mild	7 mild
Nausea/pain	5 mild	5 mild
Vomiting/diarrhea	–	–
Asthma	–	–
Generalized urticaria	–	–
Anaphylaxis	–	–
Total	45 episodes	51 episodes
	55% patients	56% patients
	6.6/1000 doses	6.3/1000 doses

description of anaphylactic reactions with multiple allergens (1, 2), although in these reports, more than three unrelated allergens (nonstandardized in one case) were used. In the population herein considered, no difference in the type and characteristics of side-effects was seen according to the number of allergens used (one or two). 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). Our conclusion is that SLIT with a limited number of mixed allergens does not increase the risk of side-effects, if the treatment is correctly prescribed and standardized extracts are used.

*Allergy & Respiratory Diseases
Department of Internal Medicine
Padiglione Maragliano
L.go R. Benzi 10
16132 Genoa
Italy
Tel.: + 39 10 3538908
Fax: + 39 10 3538904
E-mail: passalacqua@unige.it

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High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis

K. Kontou-Fili*

Key words: Hymenoptera; immunotherapy; mastocytosis; Omalizumab; venom.

Pure venom immunotherapy (VImRx) is associated with adverse reactions, particularly in individuals with mastocytosis, occasionally leading to treatment withdrawal (1). The present report refers to a patient suffering from indolent systemic mastocytosis and multiple reactions during VImRx; his treatment progressed without further adverse events on high-dose omalizumab pretherapy, administered 1 week to 1 h earlier.

High dose, 7-day to 1-h omalizumab pretreatment controls recurrent venom immunotherapy reactions in mastocytosis.

N.A., a 45-year-old man, with a near fatal anaphylactic reaction to a bee sting, was observed to suffer from indolent systemic mastocytosis [serum tryptase (42.5 μg/l, UniCAP Tryptase Pharmacia/Upjohn), a positive Tc99m-MDP bone san, as well as bone marrow biopsy]. Allergological evaluation (IDST and RAST; Unicap Pharmacia/Upjohn) confirmed IgE sensitization to bee venom ($W = 12 \times 25$, $F = 40 \times 70$ at 0.01 μg/ml *vs* histamine 10×18, 60×78 mm, respectively).

An inpatient modified rush VImRx scheme was initiated and patient was placed on H1 and H2 antagonist (Levocetirizine, cetirizine, dimethindene at 8-h intervals and ranitidine every 12 h.) for prophylaxis because of frequent adverse reactions. VImRx was progressed slowly to a cumulative dose of 150–200 μg in three to four divided doses at 28-day intervals. Mild-to-moderate reactions occurred 20- to 30-min postinjection in all but one, session; when there was a severe one at 18 months of VImRx that led to a trial of omalizumab; patient gave written informed consent.

One week prior to the subsequent monthly schedule of VImRx course, the patient received 300 mg omalizumab s.c. – twice the recommended dose based on weight (84 kg) and IgE (62 KU/ml) – without adverse events. Seven days later, he tolerated a cumulative dose of 150 μg venom (double the previous month's reduced dose) without any reaction. The same procedure was repeated successfully a month later and H1–H2 antagonists were discontinued. Omalizumab was administered at progressively shorter intervals, until 1 h between the two treatments was reached (Fig. 1). Patient tolerated the single 100 μg maintenance dose (never achieved before) without adverse events.

Serum tryptase measurements showed a progressive reduction (Fig. 1) and IDST, repeated at 8 months, 3×2 mm erythema at 1 μg/ml of venom. Two and three weeks later patient tolerated single stings by unknown Hymenoptera. Heat-induced flushing – the only subjective complaint of mastocytosis – ceased to be a problem, even at temperatures exceeding 45°C.

Omalizumab, the humanized m-antibody to the Fcε, blocks the binding of free IgE to its corresponding FcεRI on basophil and mast cells, thus inhibiting their activation by allergens. Furthermore, it causes rapid reduction in the FcεRI expression by basophils (2) and a slower one by dermal mast cells (3), while it exerts additional immune-modifying effects.

Omalizumab, administered 9 weeks before rush pollen immunotherapy, significantly reduced reactions (4), while unprovoked anaphylaxis was aborted in two systemic mastocytosis patients (5).