

ORIGINAL ARTICLE

A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy

M. Schiappoli^{*}, E. Ridolo[†], G. Senna^{*}, R. Alesina[‡], L. Antonicelli[§], R. Asero[¶], M. T. Costantino^{||}, R. Longo^{**}, A. Musarra^{††}, E. Nettis^{‡‡}, M. Crivellaro^{§§}, E. Savi^{¶¶}, A. Massolo^{|||} and G. Passalacqua^{***}

^{*}Allergy Unit, Verona General Hospital, Vienna, Austria, [†]Department of Clinical Sciences, University of Parma, Parma, Italy, [‡]Respiratory Diseases, University of Pavia, Pavia, Italy, [§]Allergy Unit, Riuniti Hospital, Ancona, Italy, [¶]Allergy Unit, San Carlo Clinic, Paderno Dugnano, Milan, Italy, ^{||}Allergy Unit, Poma Hospital, Mantova, Italy, ^{**}Allergy Unit, National Healthcare, Tropea, Italy, ^{††}Allergy Unit, National Healthcare, Reggio Calabria, Italy, ^{‡‡}Allergy and Clinical Immunology, University of Bari, Bari, Italy, ^{§§}Allergy Unit, University of Padua, Padua, Italy, ^{¶¶}Allergy Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy, ^{|||}Department of Ecosystem and Public Health, Faculty of Veterinary Medicine, University of Calgary, Canada and ^{***}Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy

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Summary

Background Subcutaneous immunotherapy is effective for the treatment of respiratory allergy, and it is largely used in Italy, but no systematic safety assessment has been carried out so far.

Objective To assess prospectively the safety of injection immunotherapy in a multicentre, real-life survey.

Methods Eleven Italian allergy departments recorded the clinical characteristics of systemic reactions (SRs) due to immunotherapy. Vaccines were prescribed according to guidelines; only standardized depot extracts were used. SRs were graded according to the EAACI recommendations, and were classified as immediate or delayed.

Results One thousand seven hundred and thirty-eight patients (847 males, age range 5–71) received immunotherapy from eight different manufacturers, for a total of 2038 courses (300 patients received two extracts). A total of 60 785 injections were given over a mean immunotherapy duration of 3 years. Overall, 95 reactions were observed in 57 patients (3.28%), corresponding to 4.7% of the courses and 1.56/1000 injections. Twenty-five patients experienced more than one adverse event. There were 34 grade 2, 60 grade 3 and one grade 4 reactions and no fatality. SRs occurred more frequently in patients with asthma than in patients with rhinitis alone (4.1% vs. 1.1%), and were equally distributed between the build-up and the maintenance phase. Ragweed and grass extracts caused significantly more side effects than other allergens.

Conclusion In this large prospective study, the rate of SRs was low, thus confirming that injection immunotherapy has an acceptable risk/benefit ratio when prescribed and carried out according to recommendations.

Keywords respiratory allergy, safety, subcutaneous immunotherapy, systemic reaction

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Correspondence:

Giovanni Passalacqua, Allergy & Respiratory Diseases, Department of Internal Medicine, Padiglione Maragliano, Lgo R. Benzi 10, 16132 Genoa, Italy.
E-mail: passalacqua@unige.it

Introduction

Allergen-specific immunotherapy (SIT) is the only treatment able to change the natural history of allergic rhinitis and asthma, and of hymenoptera venom allergy [1–3]. Subcutaneous immunotherapy (SCIT) was introduced on an empirical basis about one century ago, and its use spread rapidly. Nevertheless, a clear definition of indica-

tions, contraindications and practical rules to follow has been established only in the recent years [1]. It is now unanimously recognized that SCIT reduces the symptoms of respiratory allergy during the natural exposure, improves the quality of life and may prevent the progression towards asthma, but the problem of adverse reactions still remains the major drawback of this treatment. Although the risk of life-threatening reactions or even fatalities due

to SCIT is known since the middle of the 20th century, and several reports of adverse reactions appeared in the early 1980s, retrospective safety data based on questionnaires began to be systematically collected only some years later in the USA [4–8]. Of note, in 1986, the British Committee on the Safety of Medicines reported 26 deaths certainly due to SCIT and imposed such severe restrictions that the treatment was virtually abandoned in Great Britain [9].

The large surveys performed in the United States recorded 58 deaths over a 50-year period, with a risk of one death every 2 500 000 injections and one near-fatal reaction per million injections [4–8]. However, while a fatal reaction can be considered the tip of the iceberg, systemic reactions (SRs) (including near-fatal or life-threatening ones) represent the critical aspect in the risk/benefit evaluation of injection immunotherapy. In the studies published so far, the frequency of SCIT-induced SRs is largely variable according to the allergen used, the administration schedule, the standardization of the extract, the maintenance dose given and the severity and type of disease before the treatment [8, 10–12]. Another problem in reporting SRs is the lack of a universally accepted classification/grading of the adverse events. Finally, most data on systemic side effects come from small controlled studies, whereas only large-scale surveys can assure reliable data on the prevalence, nature and severity of side effects. Different from the United States, where surveys are regularly performed among specialists, in Europe, there have been only a few studies on safety, some of which included only small numbers of subjects [13–17].

Because the occurrence of SRs depends on a number of factors, including the local cultural background and available extracts, the results obtained in a single centre cannot be easily extrapolated to all countries and realities. For this reason, we undertook a multi-centre Italian prospective survey to assess the safety and the risk factors for SRs in patients treated with SCIT for respiratory allergies.

Methods

Eleven allergy departments in Italian hospitals (Ancona, Bari, Genoa, Mantova, Milan, Parma, Pavia, Piacenza, Reggio Calabria, Tropea and Verona) were involved in this prospective survey, which started in January 2003 and ended in December 2006. Physicians working at each centre were asked to record in a standardized form all the prescribed SITs for respiratory allergy (rhinitis and/or asthma) and the adverse events observed during the course of treatments.

Immunotherapy was prescribed according to the recommendations of the ARIA document and of the World Health Organization [1, 2]. Allergy to mite and/or pollens was defined by means a typical case history, a positive skin prick test and/or the presence of specific serum IgE.

The diagnosis and severity of asthma and rhinitis were established according to GINA and ARIA guidelines [2, 18], respectively.

There was no restriction on the treatment prescribed, and each centre used the preferred commercial products. Only standardized allergen extracts with depot formulation (adsorbed on aluminium hydroxide or on calcium phosphate) were used for SIT. Patients could be treated with either mite and/or pollen vaccines, but these allergens were never mixed in the same injection. The build-up phase was carried out according to the schedule provided by the manufacturer. Weekly injections were administered to reach the top tolerated dose, and then the maintenance dose was given on a monthly basis. In the case of pollen vaccines, the maintenance dosage was reduced by 50% during the pollen season. The dose was also reduced in the case of SRs, troublesome immediate and/or delayed large local reactions or exceeding interval between two consecutive injections (> 6 weeks). After each injection, patients were kept under observation for 30 min by nurses and/or physicians. Allergen extract dosage, change in therapy and SRs were recorded. Peak expiratory flow was also recorded before and after injection in asthmatic patients.

Patients with SRs were kept under further observation, and appropriate rescue treatments were given. SRs were subdivided into immediate (occurring within 30 min) and late SRs (debut after 30 min). The severity was graded based on the symptoms and response to rescue medication, according to the EAACI classification [19] revised by the World Health Organization [1], as follows: grade 0: no symptoms; grade 1: non-specific symptoms probably non-IgE-mediated; grade 2: (mild): mild rhinitis or asthma responding to antihistamines or β -2 bronchodilators; grade 3: (non-life-threatening): urticaria, angio-oedema or severe asthma, responding to the treatment; grade 4 (anaphylactic shock), e.g. rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction (or hypotension or collapse) requiring intensive treatment.

At each SR, a detailed recording of demographic and clinical characteristics of the patient, as well as of the characteristics of SCIT course was performed. This included details on the dose, the batch, the phase of treatment and the presence of risk factors (infections, concomitant drugs, exposure to allergens, alcohol intake, etc.). The course of the SR and the actions taken were recorded as well.

Statistical analysis

The database was analysed for descriptive statistics by means of the SAS[®] software (SAS Institute, Italy, Milan). The means, standard deviations and percentages were calculated. The analysis of SRs according to sex, age, presence of asthma, allergen and manufacturer was carried out by appropriate logistic regression applied to

contingency tables (χ^2 -test, Fisher's exact test). Odds ratio (OR) and relative risk (RR) with 95% confidence intervals are reported.

Results

Up to December 2006, 1738 patients (847 males and 891 females, age range 5–71) received SCIT at the 11 participating centres. Five hundred and four patients (29%) suffered from allergic rhinitis alone and 1234 (71%) from asthma with or without allergic rhinitis. Rhinitis was moderate/severe in all cases and asthma was intermittent to moderate. The prescribed allergen extracts were: 534 grass, 444 mite, 389 parietaria, 319 trees, 309 ragweed and 43 others (cat, alternaria and cypress), for a total of 2038 treatments. Three hundred patients (17.3%) received two extracts. A total of 60785 injections were administered. All the treatments were given on a continuous basis, and the average duration was 36 months. The manufacturers were: Allergy Therapeutics, Milan, Italy (52 vaccines); ALK-Abelló Italy, Lainate, Milan, Italy (481 vaccines); Anallergo, Florence, Italy (71 vaccines); HAL Allergy Italy, Rome, Italy (37 vaccines); Lofarma Allergeni SpA, Milan, Italy (182 vaccines); Allergopharma (Merck), Milan, Italy (349 vaccines); Sarm Allergeni, Guidonia, Rome, Italy (10 vaccines) and Stallergenes Italy, Milan, Italy (856 vaccines).

Overall, 95 SRs were recorded in 57 patients (3.28%), 24 males and 33 females, mean age 31.1 years, corresponding to 4.7% of the SCIT courses and 1.56/1000 injections. Out of the 57 patients, 32 experienced one single adverse event, whereas the remaining 25 patients accounted for 63 reactions (16 patients with two SRs, six with three, two with four and one with five SRs). Age, sex or disease (rhinitis/asthma) did not represent risk factors for having multiple SRs. No SR occurred in those patients receiving more than one extract. There were 34 grade 2, 60 grade 3 and one grade 4 reaction and no fatality. There was no association between age decades or sex and SRs. On the contrary, SRs occurred in 4.1% of asthmatic patients and in 1.1% of rhinitis patients; thus, the presence of asthma represented a significant risk factor, as detailed in Table 1. Overall, SRs (number of patients and of reactions) were equally distributed between the build-up and the maintenance phase. In particular, the build-up phase did not represent a risk factor for SRs [OR = 0.82 (0.54–1.23); RR = 0.86 (0.5–1.2); P = NS]. Similarly, immediate- and late-onset SRs occurred with a comparable frequency (Table 2). Looking separately at the grades of severity, only grade 2 SRs in the maintenance phase were significantly (P = 0.04) more frequent (Fig. 1). The only grade 4 reaction was immediate and occurred during the build-up phase. Late reactions (onset > 30 min after administration) were only grade 2 or 3 and always occurred after the patient had left the hospital (45 min to 24 h). Some of the

Table 1. Demography and clinical characteristics of the subjects with or without SRs

	Patients with SR (N = 57)	Patients without SR (N = 1681)	P
Age	29.0 ± 15.6	33.3 ± 18.1	NS for all decades
Sex (m/f)	24/33	823/858	NS
% Male	42.1	48.9	OR = 0.76 (0.44–1.29) RR = 0.99 (0.97–1.1)
Asthma (%)	51 (89%)	1183 (70.3)	0.01
Rhinitis alone (%)	6 (11%)	498 (29.7)	OR = 3.57 (1.5–8.4) RR = 1.04 (1.01–1.05)

OR, odds ratio; RR, relative risk; SRs, systemic reactions; m, male; f, female.

Table 2. Characteristics of the patients with SRs

		P
Asthma	No asthma	
51/1234 (4.1%)	6/504 (1.1%)	0.03
Female	Male	
33/1738 (1.9%)	24/1738 (1.4%)	NS
Build-up – patients	Maintenance – patients	
28/57 (49.1%)	29/57 (50.9%)	NS
Build-up – reactions	Maintenance – reactions	
43/95 (45%)	52/95 (55%)	NS
Immediate onset – patients	Late onset – patients	
33/57 (57%)	24/57 (43%)	NS
Immediate onset – reactions	Late onset – reactions	
42/95 (44%)	53/95 (56%)	NS

SRs, systemic reactions.

patients returned to the clinic for treatment while other SRs were managed by the patient's GP or even spontaneously resolved. Urticaria (with/without angio-oedema), rhinitis or asthma accounted for most SRs, either late or immediate, and there was only one case of anaphylactic shock. Epinephrine was used in four patients (one anaphylaxis, two severe asthma and one asthma with generalized urticaria). In subjects with seasonal allergic rhinitis/asthma, 93% of reactions occurred out of the pollen season. The clinical characteristics and the management of the SRs are summarized in Table 3.

According to the allergen used, SRs occurred as follows: ragweed 8.1%, grass 4.2%, mite 1.3%, parietaria 0.7% and birch 0.3%. Thus, the logistic regression analyses showed that ragweed extracts [OR = 5.032 (2.9–8.6); RR = 1.08 (1.06–1.10); P = 0.01] and grass extracts [OR = 1.8 (1.04–3.1); RR = 1.02 (1–1.04); P = 0.04] were significantly associated with SRs, as shown in Fig. 2. Among the manufacturers, the percentage of SCIT causing SRs ranged between 0% and 5.4%, as shown in Table 4. Looking at the absolute number of SRs, only one extract was associated with a slightly but significantly higher risk of SR [OR = 2.3

(1.3–4.08); RR = 1.033 (1.05–1.06); $P = 0.048$], as summarized in Fig. 3, and in this case, the grass extract accounted for 68% of reactions.

Discussion

Although SRs are not common and fatalities are exceptional, the safety still remains the most relevant problem with SCIT. Moreover, even when the safety recommendations are followed, a fraction of SRs remain unavoidable

and unpredictable. There are several US surveys on the safety of SCIT, but few in Europe, providing results that vary according to the recording system, the country and the schedule utilized. Although sublingual immunotherapy is largely used, in Italy, SCIT still accounts for about 30% of the total immunotherapy market [20]. Therefore, there was a need to assess the safety of SCIT in a realistic manner. For this reason, we undertook this prospective post-marketing survey involving several allergy centres over the national territory.

Altogether, the results of this survey suggest that SCIT is safe, since SRs occurred only in 3.6% of patients and 0.15% of injections, with only one grade 4 reaction per >2000 courses. This is in accordance with other studies carried out in Europe. In two previous Italian

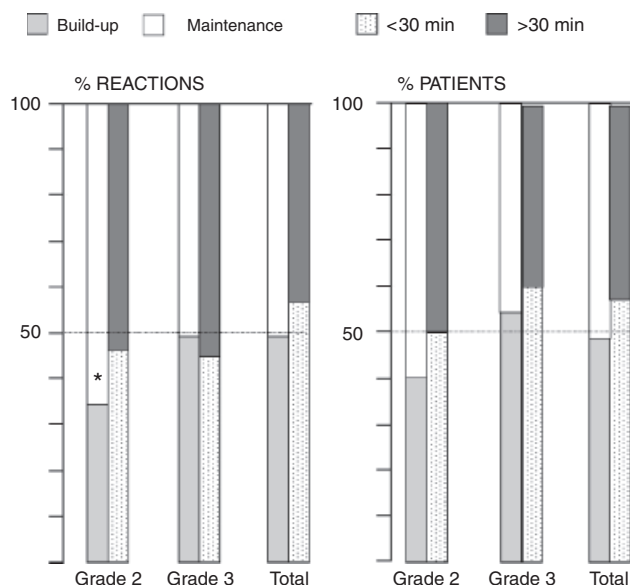


Fig. 1. Percentage of systemic reactions (SRs), and percentage of patients with SRs according to the time of onset (immediate/delayed) and to the phase of the treatment (build-up/maintenance). Grade 2, grade 3 and total are shown separately. The asterisk indicates a significant difference (<0.05).

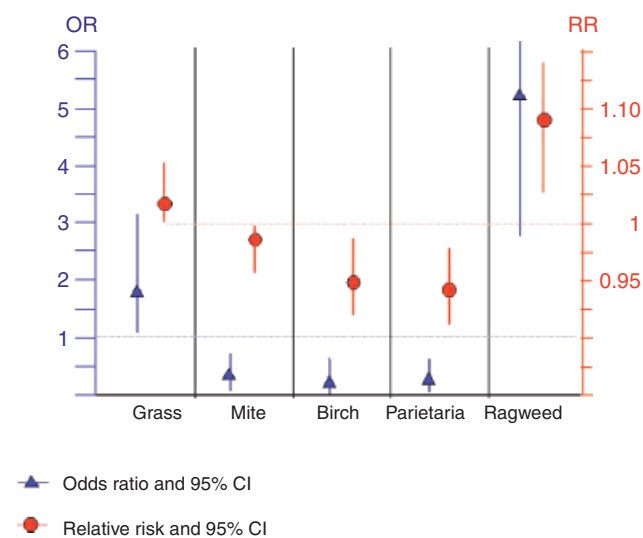


Fig. 2. Relative risk (right axis, circles) and odds ratio (left axis, triangles) for the association between the single allergens and systemic reactions. The vertical lines represent the 95% confidence interval.

Table 3. Characteristics of the SRs

Symptoms	Number of patients	Number of SRs	Onset time		Phase		Actions taken
			< 30 min	> 30 min	Maintenance	Build-up	
Urticaria w/w angio-oedema	25	48	24	24	23	25	None or antihistamine with/without oral or i.v. steroid
Rhinitis only	12	16	9	7	11	5	None or antihistamine
Mild asthma*	10	18	6	12	11	7	Inhaled albuterol
Asthma and urticaria	7	10	6	4	6	4	Albuterol+i.v. steroid+antihistamine (adrenaline in one patient)
Severe asthma	2	2	2	0	1	1	Albuterol+i.m. adrenaline+i.v. steroid+oxygen
Anaphylaxis	1	1	1	0	0	1	Albuterol+i.m. adrenaline+i.v. steroid+oxygen+i.v. saline
Total	57	95	48	47	52	43	

*With/without rhinitis (grade 2).

SRs, systemic reactions.

Table 4. SRs according to the manufacturer

	Number of SCIT	Number of SCIT with SRs	% SCIT with SRs	Number of reactions per extract				
				Grass	Ragweed	Pariet	Mite	Birch
Allergy therapeutics	52	1	1.9	1	–	–	–	–
ALK Abelló Italy	481	9	1.9	3	4	1	1	–
Anallergo	71	0	0	–	–	–	–	–
HAL Allergy Italy	37	0	0	–	–	–	–	–
Lofarma Allergeni SpA	182	2	1.1	1	–	1	–	–
Allergopharma (Merck)	349	19	5.4	13	3	1	1	1
Sarm Allergeni	10	0	0	–	–	–	–	–
Stallergenes Italy	856	26	3.0	4	18	–	4	–
Total	2038	57	2.8	22	25	3	6	1

SRs, systemic reactions; SCIT, subcutaneous immunotherapy.

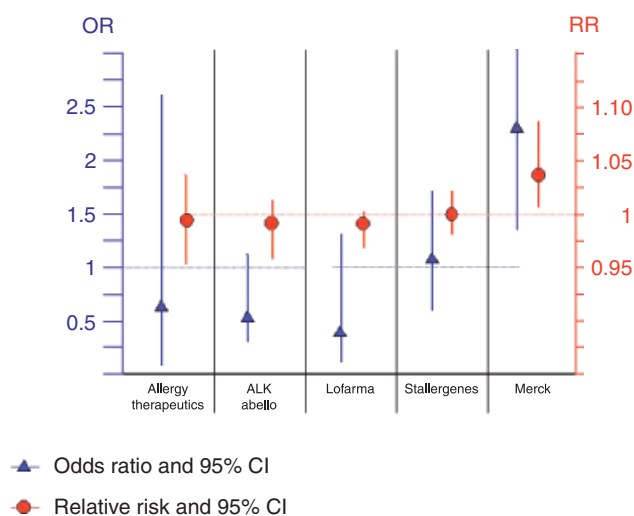


Fig. 3. Relative risk (right axis, circles) and odds ratio (left axis, triangles) for the association between the manufacturers and systemic reactions. The vertical lines represent the 95% confidence interval.

surveys [13, 16], the overall rates of SRs per patient and per injection were 5.2% and 0.09%, and 5.2% and 0.6%, respectively. In a Spanish survey including 423 patients, Moreno et al. [14] found a slightly lower prevalence, i.e. 3.7% reactions per patient and 0.3% per injection. A higher frequency of SRs has been reported using aqueous extracts [7, 21] or accelerated schedules of treatment [4, 5]. In the present study, all centres used depot extracts and a prolonged build-up phase, and this is probably one of the reasons for the low occurrence of SRs. On the other hand, rush and cluster regimens should be considered as a first choice only when it is mandatory to reach the maintenance dose as soon as possible, such as in patients living far from hospital or in those with hymenoptera allergy. Most SRs, both immediate and late, presented clinically as asthma, urticaria and rhinitis and could be satisfactorily managed by an appropriate pharmacological treatment, epinephrine being used only in four cases.

Late reactions, occurring after the patient had left the hospital, were only grade 2 or 3 ones. Thus, the recommended waiting period of 30 min [22] seems to be appropriate in terms of safety.

In contrast with other reports [23, 24], in this study, SRs were almost equally distributed between maintenance and build-up phases. This highlights the importance of keeping patients carefully controlled during the whole treatment, and not just in the build-up phase. Treatments with multiple extracts did not represent a risk factor for SRs in our study, since none of the patients receiving more than one vaccine had adverse events. This could be attributed to the fact that no more than two extracts per patient were used, and that allergens were never mixed in the same injection. In our study, 25 patients had multiple reactions, suggesting that certain individuals may be more prone to developing SRs. Age, sex and disease were not associated to multiple reactions, but our database did not allow to identify other specific individual risk factors. On the other hand, we confirmed that the presence of asthma is a significant risk factor for SRs. This is in agreement with the majority of previous surveys [4, 6, 23], although a recent retrospective study [25] found no significant association between SRs and the presence of asthma. Ragweed and grass extracts were responsible for the large majority of SRs, and this is in agreement with other data concerning pollen immunotherapy [26]. Whether this is caused by a higher IgE reactivity of patients with these types of airborne allergies or depends on a higher amount of major allergens in extracts remains to be established, also because the allergen content in commercial extracts is still largely variable [27]. In this regard, we could notice that with Merck-Allergopharma extracts, grass accounted for 68% of SRs, and with Stallergenes extracts ragweed accounted for 69% of the SRs, suggesting that those extracts may have a high allergenic potency.

In conclusion, the low rate of SRs observed in this large prospective study suggests that SCIT has an acceptable risk/benefit ratio, provided that it is carried out following

the recommendations and according to the manufacturers' instructions.

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