

RESEARCH ARTICLE

Safety of subcutaneous immunotherapy with inhalant allergen extracts: a single-center 30-year experience from Turkey

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Abstract

Context: Although subcutaneous allergen immunotherapy (SCIT) is effective in allergic rhinitis (AR) and asthma, it carries a risk of local and systemic adverse reactions.

Objective: The aim of this study was to evaluate the rates and clinical characteristics of local and systemic reactions (LR and SR), and to identify their relation of demographic features, allergen extracts and diagnosis.

Materials and methods: This study analyzed the administration of SCIT from 1983 to 2013; involving 1816 patients affected by allergic asthma and/or AR.

Results: The rates of SR from SCIT were 0.078% per injection and 9% per patient. According to the World Allergy Organization 2010 grading system, 91 grade 1 reactions (44%), 67 grade 2 reactions (32.3%), 33 grade 3 reactions (16%) and 16 grade 4 reactions (7.7%) were seen. There was no fatal outcome from any of the SRs. Risk factors for a SR included: aluminium-adsorbed extract, pollen-containing vaccines, large LR and recurrent (≥ 2) LR. The total LR rates were 0.062% per injection and 5.2% per patient; the small LR rates were 0.027% per injection and 2.3% per patient, and the large LR rate were 0.035% per injection and 2.9% per patient. Female gender, depot extracts, calcium phosphate-adsorbed extract and pollen vaccines were identified as risk factors for LR.

Conclusion: The analysis of our data over a 30-year period confirmed that SCIT with inhalant allergens conducted strictly according to the standard protocols and when administered by experienced staff is a safe method of treatment with only a few side-effects.

Keywords

Inhalant allergens, local reaction, risk factors, subcutaneous allergen immunotherapy, systemic reaction

History

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Introduction

Subcutaneous allergen immunotherapy (SCIT) has been widely used by physicians as the treatment of allergic diseases since it was introduced by Noon and Freeman^{1,2}. Along with allergen avoidance, immunotherapy is a unique etiology-based treatment for allergic diseases. Even though it has been accepted as a safe method of treatment, there is a risk of side-effects. Local reactions (LRs) and systemic reactions (SRs) are well-described complication of SCIT³. The fear of the side-effects of SCIT, substantial costs, prolonged injection schedule and patients' non-compliance are the burdened of this treatment method⁴.

There are many risk factors for local and systemic reactions. Although several studies have identified these factors, such as patient characteristics, type of allergen extracts, injection phase/season, there are still some controversies (e.g. frequency and severity of adverse reactions)

about immunotherapy safety^{5–9}. Heterogeneity of the study population, variability in the schedules and some other reasons, such as different injection techniques, can cause these different results.

The aims of this study were to evaluate the frequency of local and systemic reactions due to subcutaneous aeroallergen immunotherapy in our clinic over a 30-year period, and to identify factors associated with increased risk of local and systemic reactions.

Methods

Study design

Between 1983 and 2013, a total of 1816 patients admitted to our division to receive SCIT for respiratory hypersensitivities were analyzed in this retrospective study. The study was approved by the Gulhane Military Medical Academy and School of Medicine Ethics Committee. The data were collected from the patient charts including the injection records, medication records and physician notes, systemic (SR) and local (LR) reaction records.

Twenty-two patients, receiving two or more injections and also have SRs per injection visit were excluded from the study, because the extract causing the SR was unknown.

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In addition, the patients receiving venom immunotherapy were not included in the study.

The clinical responses to immunotherapy were evaluated by allergist with physical examination and standard symptom questionnaire at the first year of treatment. Decision to go on maintenance immunotherapy was based on patient clinical response, adverse reaction history, disease severity and marked reduction in requirements for anti-allergic medications, such as nasal/inhaled steroids, antihistamines.

Immunotherapy protocol

Between 1983 and 2003, aqueous extracts (Greer Laboratories Inc., Lenoir, NC) were used in SCIT. Immunotherapy with aqueous extract started with a dose of 0.1 ml at a concentration of 10 AU/ml for mites and 1/200 000 wt/vol for pollens and molds was administered twice weekly. After this build-up period (12–16 week), maintenance therapy was given. Maintenance period was consisted of 0.5 ml of the 2000 AU/ml for mites, or 0.5 ml of the 1/200 wt/vol for pollens and molds, administered during the subsequent 192 weeks and discontinuation at the end of the 4th year.

A standardized depot allergen extracts (pollens, molds and cat epithelia) adsorbed onto aluminium hydroxide (Novo-Helisen Depot, Allergopharma Inc., Reinbek, Germany) or calcium phosphate (Phostal, Stallergènes, Antony, France) were used for SCIT between 2003 and 2013. Twelve-week build-up phase (weekly injections) of the immunotherapy with Novo-Helisen Depot (NH) and Phostal (P) was started at a three consequently dose of 0.1–0.8 ml of 50 TU/ml(NH); 0.1 IR/ml (P) (weeks 1–3); 0.1–0.8 ml of 500 TU/ml(NH); 1 IR/ml (P) (weeks 4–8) and 0.1–0.8 ml of 5000 TU/ml (NH); 10 IR/ml (P) (weeks 9–12).

The dose of 0.8 ml/5000 TU/ml (NH) and 0.8 ml/10 IR/ml (P) was used as a maintenance dose. The injection intervals were increased gradually to 4–6 weeks and continued for 4 years.

Each immunotherapy protocol consisted of a single injection containing the allergens to which the patient was sensitive. Antigens from different vials were not combined in a single syringe. The dose modifications were made based on several variables (i.e. new vials, missed injections or a previous large local reaction (LLR) causing discomfort).

In our clinical practice, SCIT was performed according to strictly standard policies. All patients were evaluated by an allergist before each injection and observed for at least 30 min after the injection and any signs of adverse reactions were recorded in detail on the standardized patient's chart. Adequate emergency medications and equipment to promptly treat an anaphylactic reaction were readily available. Patients were also questioned before each injection about their post-injection problems.

The skin was wiped with an alcohol swab before giving the injection. The subcutaneous injections were given in the posterior portion of the middle third of the arm at a 45- or 90-degree angle with a 26–27-gauge, insulin or tuberculin syringe at the allergy clinic. To reduce the risk of SR, the syringe was aspirated to check for blood return before injecting. If blood is present in the aspirate, the syringe was

removed and another dose was given into a new syringe to a different site. Mild pressure was applied to the injection site at least 1 min immediately after removal of the needle.

Definitions of local and systemic reactions

Erythema and/or swelling at the injection area were defined as LLR (≥ 5 cm in diameter) and small local reaction (SLR) (≥ 5 mm to < 5 cm in diameter) within the first 30–45 min after injection. Delayed LLR (1 h or more) was reported by the patient at the following SCIT visit.

The signs and symptoms of SRs and also their response to the treatment recorded on patient charts are adapted and graded according to the universal grading system, proposed by the World Allergy Organization¹⁰: Grade 1: Symptoms of one organ system (cutaneous, upper respiratory tract, conjunctival, gastrointestinal, other symptoms, such as nausea, headache), Grade 2: Symptoms of more than one organ system or gastrointestinal symptoms or asthma symptoms/signs which respond well to inhaled bronchodilators, Grade 3: Asthma symptoms/signs which do not respond to inhaled bronchodilator or upper respiratory tract (laryngeal, uvula, tongue) edema with or without stridor and Grade 4: Respiratory failure or hypotension; with or without loss of consciousness. LRs (small and large local) and SRs were documented in the immunotherapy chart for each patient at each visit by the allergist who administered the injection.

Statistical analysis

Data were analyzed with SPSS statistical software, version 22 (SPSS Inc, Chicago, IL). In the first step of statistical evaluation, patients' characteristics were totally determined. Thereafter, we subdivided the patients according to the gender, diagnosis, extract/adjuvant types and each subgroup was compared in its own. Continuous measures were described as means and standard deviations for normally distributed data and median percentiles for non-normally distributed data. Categorical measures were summarized using frequencies and percentages. Chi-square, Fisher's exact and logistic regression tests were used in evaluating the comparisons among the variables and the relationships of the groups. Differences were considered significant at $p < 0.05$, 95% confidence interval was calculated for the rates of LR and SRs. ANOVA test with Bonferroni correction tests was used for multiple comparison of the number of injections in patients grouped as SLR, LLR and SR status.

Results

Patients' demographic and clinical characteristics

In total, 1816 patients (993 males, [54.7%], 823 females [45.3%]), including 1114 with allergic rhinitis (AR), 194 with asthma and 508 with asthma plus AR who underwent aeroallergen immunotherapy from study period, were analyzed in this study. The mean age ($\pm$ SD) of patients was 25.7 ± 12.2 years. The average duration of immunotherapy was 35.3 months. All patients had a positive skin prick test for inhalant allergens (pollens, dust mites, molds, cockroach and cat epithelia). Of these, 1574 patients were monosensitized and 242 patients were polysensitized.

Table 1. Distribution of the allergen extracts used in immunotherapy.

Treatment antigens	(n)				Total
	Pollen	HDM	Mold	Cat	
Aqueous extract	1393	491	28	3	1915
Standardized depot					
Novo-Helisen Depot	59	29	1	1	90
Phostal	89	20	0	0	109
Total	1541	540	29	4	2114

HDM, house dust mite.

Table 2. Outcomes of SCIT according to main factors.

	(%)				
	Completed	SR ^a	LR ^b	Discontinued	Others ^c
Gender					
Male	75.9	2.9	0.2	0.3	20.6
Female	82.3	3	1	0.9	12.9
Diagnosis					
Allergic rhinitis	78.4	2.8	0.7	0.7	17.3
Asthma	85.6	0.5	0	0	13.9
Asthma + Allergic rhinitis	77	4.2	0.4	0.4	18
Extract type					
Aqueous	79.6	2.8	0.3	0.5	16.8
Depot	75.7	1.3	2.6	0.7	19.7
Adjuvant type					
Aluminium	75.8	3	1.5	1.5	18.2
Calcium phosphate	75.6	0	3.5	0	20.9
Allergen type					
Mite vaccines	81.1	2.1	0	0	16.8
Pollen vaccines	78.3	2.9	0.7	0.7	17.4

LR, local reaction; SCIT, subcutaneous immunotherapy; SR, systemic reaction

^aSCIT stopped due to systemic reactions.^bSCIT stopped due to local reactions.^cSCIT stopped due to personal reasons.

Patients' treatment characteristics

Over 30 years, a total of approximately 262 300 allergen immunotherapy injections were administered in a 2114 SCIT protocols, of which 1915 were aqueous and 199 were standardized depot extracts. The distribution and contents of allergen extracts are shown in Table 1.

Table 2 shows the treatment outcomes in terms of gender, diagnosis, extract and adjuvant types. One thousand five hundred and seventy-five (86.7%) (801 male and 774 female) patients completed the immunotherapy. Immunotherapy was discontinued in 10 patients (0.6%) (three male and seven female) because of poor response to therapy after one year of treatment. SCIT was also stopped by the allergists in 63 patients due to adverse reactions (SR: 53 patients [2.9%] [29 male and 24 female]; LLR: 10 patients [0.6%] [two male and eight female]). Up to 168 patients (9.2%) (148 poor compliance, 17 pregnancy, three loss of social security) withdrawn, due to personal reasons not related to SCIT.

Systemic reactions

A total of 207 SRs were recorded in 165 patients for a rate of 0.078% per injection and 9% per patient. Twenty-seven patients experienced two SRs and seven patients experienced three SRs. Of these, 95 (57.5%) patients completed the

immunotherapy. In accordance with the WAO position paper, there were 91 grade 1 reactions (44%), 67 grade 2 reactions (32.3%), 33 grade 3 reactions (16%), and 16 grade 4 reactions (7.7%). No fatality due to SRs was observed in 30 years.

Systemic reactions mostly occurred in the second decade of life, for a rate of 13.8% per patient. The majority of SRs were developed in summer (39.3%). A hundred and thirty-two (64.1%) SRs occurred during the build-up phase of immunotherapy. With regard of extract type, a SR mostly appeared during the build-up phase in aqueous extracts (65.3%), but in maintenance phase in depot extracts (53.8%). The SR rate was higher in pollen-containing aqueous extracts than all other extracts (aqueous, depot) (11.9%).

There was no significant statistical difference in the SR rates between the male (8.6%) and female patients (9.7%, $p=0.413$). The rate of SR in asthma plus AR patients (11%) was higher than asthma (1.5%) and AR patients (9.5%). The risk of SR was lowest for asthmatic patients than in patients with asthma plus rhinitis (OR, 0.13; 95% CI, 0.04–0.41; $p<0.001$), or (OR, 0.15; 95% CI, 0.05–0.48; $p<0.001$) AR patients (Table 3).

There was no significant difference in the SR rates between the aqueous (10.3%) and depot allergen extracts (8.2%, $p=0.49$). As an interesting fact, grade 1 SR rate was higher in depot extract (5.1–3.1%) but grade 2 (5.4–2.5%), grade 3 (1.7–0.6%) and grade 4 SRs (0.63–0%) frequencies were higher in aqueous extracts. When we compared the pollen- and mite-containing extracts (aqueous and depot) for the rate of SR, we found that pollen vaccines had a higher ratio of SRs than mite vaccines (OR, 2.21; 95% CI, 1.48–3.31; $p<0.001$) (Table 3).

With respect to adjuvant type, the frequency of SR between aluminium hydroxide- and calcium phosphate-adsorbed allergen extracts was significantly different (14.1% and 3.4% respectively) (OR, 0.21; 95% CI, 0.58–0.82; $p=0.025$) (Table 3).

The frequency of LRs was significantly higher in systemic reactors than non-systemic reactors (systemic reactors: 15.5%, non-systemic reactors: 3.9%; $p<0.001$). The number of LRs was also significantly associated with SRs. Systemic reaction rate was higher in patients who had experienced more than one LRs (OR, 3.09; 95% CI, 1.17–8.15; $p=0.022$) (Table 3).

Seventeen patients had experienced 23 LLRs and six SLRs before SRs. Characteristics and treatment outcome of these patients are shown in Table 4.

Local reactions

One hundred and sixty-four LRs (93 LLRs–71 SLRs) were seen in 94 patients for a rate of 0.062% per injection and 5.2% per patient. Female patients (7%) experienced more LRs than male patients (3.6%; OR, 2.01; 95% CI, 1.31–3.08; $p<0.001$), and also female patients (48.3%) experienced more recurrent (≥ 2) LRs than male patients (16.7%, $p=0.002$) (Table 5). Among the local reactors, 70 patients (74%) completed the treatment.

The AR patients (6.3%) had more experienced LRs than asthma (0.5%) and asthma plus AR (4.5%) patients. There was a significant difference in the LRs rates, between the depot (38.1%) and aqueous allergen extracts

Table 3. Risk factors for systemic reactions to immunotherapy.

Risk factor		OR	95% CI	p Value
Gender		1.15	(0.83–1.58)	NS
Diagnosis				
Asthma (reference)		1.00		
Allergic rhinitis		0.15	(0.05–0.48)	0.001
Asthma + Allergic rhinitis		0.13	(0.04–0.41)	0.001
Extract type (aqueous/depot)		0.78	(0.43–1.40)	NS
Adjuvant type (aluminium/calcium phosphate)		0.21	(0.58–0.82)	0.025
Pollen versus mite vaccine		2.21	(1.48–3.31)	0.001
LR (+/–)		4.55	(2.81–7.37)	0.001
LLR versus SLR		7.58	(4.29–13.40)	0.001
Number of LR (1/≥2)		3.09	(1.17–8.15)	0.022

CI, confidence interval; LLR, large local reaction; LR, local reaction; OR, odds ratio; NS, not significant; SLR, small local reaction.

(4.8%, $p < 0.001$) (Table 5). Similar to SRs, pollen-containing extracts has a higher frequency of LR compared to the mite vaccines (OR, 1.84; 95% CI, 1.20–2.82; $p = 0.005$).

The rate of LR was significantly higher in patient treated with calcium phosphate-adsorbed extracts (46%) than aluminium hydroxide-adsorbed extracts (27.2%, $p = 0.008$) (Table 5). On the other hand, recurrent LR was higher in patients received aluminium hydroxide-adsorbed extracts (71.4%) than the calcium phosphate-adsorbed extracts (34.6%, $p = 0.080$). The number of LR was significantly different between LLRs and SLRs patients. LLRs patients experienced more recurrent LR than SLRs patients (51.9–16.7%; $p < 0.001$).

Large local reactions

Overall, 93 LLRs were experienced by 52 patients, giving a LLRs rate of 2.9% of all patients and 0.035% of all SCIT injections administered during 30 years. Twenty-five of 93 LLRs (27%) were delayed. Fifty-eight percent of the LLRs were occurred during the maintenance phase. Furthermore, LLRs were more frequent in the winter (33.7%), and the fourth decade of life (4.2%). There was a higher rate of LLRs among female than male patients, which was statistically significant (males 2.2%; females 8%; OR, 3.06; 95% CI, 1.67–5.63; $p < 0.001$).

There was significant difference in the LLRs frequency, between the aqueous (3%) and depot allergen extracts (18.6%, $p < 0.001$). Among the extract types, the rate of LLRs was highest in patients treated with depot pollen extracts (21.1%). Otherwise, there was no statistical difference in the LLRs rate, between the adjuvant types (calcium phosphate, 21.2%; aluminium hydroxide, 14.8%; $p = 0.269$). Large local reactors had a higher SR rate than did non-large local reactors (large local reactors: 38.2%, non-large local reactors: 7.5%; $p < 0.001$) (Table 3).

Small local reactions

Seventy-one SLRs were occurred in 42 (2.3%) patients for a rate of 0.027% per injection. For all injections, the SLRs were mostly occurred during the buildup phase (73%), second decade of life (3%) and the winter (48.3%). The SLRs rate was almost similar between male (2.1%) and female patients (2.6%, $p = 0.538$).

SLRs rate were significantly higher in patients received a depot extracts (19.6%) than the patients received aqueous extracts (1.8%, $p < 0.001$). SLRs rate was also highest in patients received a depot pollen extracts (21.8%). Regarding adjuvant types, there was a significant difference in the SLRs rate, between the aluminium hydroxide (24.8%) and calcium phosphate-adsorbed vaccines (12.3%; OR, 2.33; 95% CI, 1.06–5.14; $p = 0.035$). The differences of frequencies of SRs were statistically not significant, between the small local reactors (11.9%) and non-small local reactors (8.3%, $p = 0.392$).

Discussion

The frequency of SRs during allergen immunotherapy varies from less than 2% to 15.9% of patients receiving conventional inhalant immunotherapy^{11,12}. The several factors by patients or treatment, can cause of these difference. Our rates of SRs (9% per patient) are comparable to other studies. In the present study, most SRs occurred in the build-up phase, similar to the results obtained by others^{12–14}. Although the difference did not reach significance, we found that slightly higher SR rate in female patients than males. Previous studies were also reported “slightly higher” SR rate in female patients^{15,16}. However, in another study, it was reported that SR rate was significantly higher in male patients¹⁷.

Previous studies described that a patients with severe or uncontrolled asthma are at increased risk for SRs to SCIT^{18–20}. We found a higher rate of SRs in patients with asthma plus AR. However, asthmatic patients have lowest SR rate. Unexpectedly, our result demonstrated that the risk of experiencing SR was 6-fold higher in rhinitis and 8-fold higher in asthma plus rhinitis than asthma. Contrary the most previous studies, there are some reports in the literature that support our results^{21–24}. Gastaminza et al. also found that the frequency of SRs was slightly higher in patients suffering rhinitis (6%) than asthma (4%)²⁵. This result may be explained by clinical heterogeneity of asthma, formulation and standardization of extracts and sensitization degree of the patient's.

A higher risk of SRs in pollen extracts than in mite extracts was found. Therefore, we focused on the distribution of allergenic type of extracts according to the diagnosis. Interestingly, we observed that the ratio of mite/pollen extract

Table 4. Demographics and characteristics of patients with local reaction preceding a systemic reaction.

	Gender	Age (yr)	Diagnosis	Immunotherapy agent	SR grade	Number of LR preceding a SR	SLR/LLR	LR phase-season	SR phase-season	Immunotherapy outcome
1.	Women	39	AR	Aqueous/Pollen	2	2	2 LLR	Buildup-Winter	Buildup-Summer	Completed successfully
2.	Women	35	AR + A	Aqueous/Pollen	2	2	2 LLR	Buildup-Autumn	Buildup-Winter	Completed successfully
3.	Women	32	AR	Aqueous/Pollen	2	2	2 LLR	Buildup-Summer	Buildup-Summer	Stopped (SR)
4.	Women	31	AR + A	Aqueous/Pollen	2	2	2 LLR	Maintenance-Spring	Maintenance-Spring	Stopped (LLR)
5.	Women	35	AR + A	Aqueous/Pollen	2	3	2 LLR + 1 SLR	Buildup-Spring	Buildup-Winter	Completed successfully
6.	Women	41	AR	Aqueous/Pollen	2	3	3 LLR	Maintenance-Autumn, Winter	Maintenance-Summer	Stopped (LLR)
7.	Men	20	AR	Aqueous/Mite	2	1	1 LLR	Maintenance-Summer	Maintenance-Winter	Completed successfully
8.	Women	33	AR + A	Aqueous/Pollen	2	1	1 LLR	Maintenance-Autumn	Maintenance-Autumn	Completed successfully
9.	Men	30	AR	Aqueous/Pollen	1	1	1 LLR	Buildup-Winter	Buildup-Summer	Discontinued (other cause)
10.	Women	17	AR	Aqueous/Pollen	1	1	1 LLR	Maintenance-Winter	Maintenance-Summer	Completed successfully
11.	Women	7	AR + A	Aqueous/Pollen	2	1	1 LLR	Maintenance-Spring	Maintenance-Summer	Stopped (LLR)
12.	Women	28	AR	Phostal/Pollen	1	1	1 LLR	Maintenance-Summer	Buildup-Summer	Completed successfully
13.	Women	37	AR	Novo-Helisen/Pollen	2	4	2 LLR + 2 SLR	Maintenance-Spring, Summer	Buildup-Summer	Completed successfully
14.	Women	17	AR	Aqueous/Pollen	1	2	2 LLR	Buildup-Winter	Maintenance-Spring	Completed successfully
15.	Men	10	AR	Aqueous/Pollen	3	1	1 SLR	Buildup-Summer	Buildup-Winter	Stopped (SR)
16.	Women	12	AR	Aqueous/Pollen	1	1	1 SLR	Buildup-Summer	Buildup-Summer	Completed successfully
17.	Men	35	AR + A	Aqueous/Mite	1	1	1 SLR	Buildup-Winter	Buildup-Spring	Completed successfully

AR, allergic rhinitis; A, asthma; LLR, large local reaction; LR, local reaction; SR, systemic reaction; SLR, small local reaction.

was highest in the asthmatic patients conversely lowest in the AR patients. Thus, it can be speculated that the distribution of allergenic type of extracts due to the diagnosis may be the reason of this unexpected result. In keeping with our study, two previous studies indicate that a higher risk for pollen vaccines than mite vaccines^{7,25}, whereas one study did not²⁶.

According to the WAO 2010 grading system¹⁰, most SRs were classified as grade 1 (44%) and grade 2 (32.3%) in this study. Furthermore, the frequency of life-threatening SRs (grades 3 and 4) constitutes 23.7% of all SRs in our study. Recently, a cross-sectional, retrospective trial involving 3732 patients reported that all SRs were of grade 1 and grade 2¹⁴. Phillips et al. also found that 44% of their SRs were grade 1 and 41% were grade 2²⁷. Additionally, they found grade 3 (6%) and grade 4 (9%) reactions in this study. Despite the relatively high frequency of potentially life-threatening reactions in the present study than previous reports, we did not observe fatal reactions due to SCIT during the study period.

Calcium phosphate and aluminium hydroxide adjuvants (depot extracts) are used in SCIT for potentiate the immune responses to allergens and to reduce adverse reactions of treatment⁹. Generally, a depot extracts were safer than aqueous extracts^{28,29}. In the present study, we found no statistical difference in SR rates between the aqueous and depot extracts, but patients treated with the aqueous extracts have a slightly high SR rate. Also, we found that more severe SRs were observed in patients treated with aqueous extracts than those of treated with depot extracts.

Since calcium phosphate is a normal constituent of the human body, it was expected that a calcium-containing extracts would be associated with fewer systemic and local reaction than aluminium-containing extracts. In accordance with this suggestion, we found statistically significant lower SR rate in patients treated with calcium phosphate-containing extracts than aluminium vaccine was used as an adjuvant. Aluminium-adsorbed extracts had a 4-fold higher risk of SRs compared with the calcium phosphate-adsorbed extracts. Furthermore, our results agree with the previous studies showing aluminium hydroxide-containing extracts was associated with a greater risk of SRs than calcium phosphate-adsorbed allergen extracts^{30,31}. In contrast, Moreno et al. found no difference between the rates of SRs, among the depot extracts (adsorbed in aluminium hydroxide or calcium phosphate)³. Calcium phosphate and aluminium hydroxide have also been used as an adjuvant with diphtheria-tetanus-pertussis vaccines. The adverse effects and efficacy of these adjuvants with this vaccine were investigated by some studies³²⁻³⁴. However, these studies have different results regarding systemic adverse effects of these adjuvants.

Previous studies have showed that LR do not predict SRs^{35,36}. Nevertheless similar to our result, it was demonstrated that systemic reactors had an increased rate of LR than non-systemic reactors in other retrospective study⁸. In other words, our study showed that LLR is a risk factor for SRs. We also found that patients experiencing recurrent LR (≥ 2) had an increased frequency of SRs compared with patients experiencing only one LR.

The reported frequency of LR per patient has been variable from 8.3% to 82%³⁷⁻⁴⁰. Our rate of LR was 5.1% and little lower when compared to these studies. Interestingly,

Table 5. Risk factors associated with local reactions.

Risk factor		OR	95% CI	p Value
Gender	Female	2.01	(1.31–3.08)	0.001
Extract type (aqueous/depot)	Depot extracts	12.26	(8.56–17.55)	0.001
Adjuvant type (aluminium/calcium phosphate)	Calcium phosphate	2.28	(1.23–4.22)	0.008
Pollen/mite vaccine	Pollen vaccines	1.84	(1.20–2.82)	0.005

CI, confidence interval; OR, odds ratio.

we found that female gender is a risk factor for LLR, but not for SLR. In the literature, although there are many factors defined that contribute to LR, to our knowledge this is the first study determining the female gender is a risk factor for LLR.

Despite claims in previous studies that depot extracts are caused fewer local side-effects, our study showed that the rate of LRs (both LLRs and SLRs) were higher in patients treated with depot extracts^{28,41}. Regarding the type of adjuvants, calcium phosphate-adsorbed extracts caused more LRs than aluminium hydroxide-adsorbed vaccines. With respect to diameter of the LRs, we observed more LLRs in patients treated with the vaccine-containing calcium phosphate adjuvant, whereas SLRs rate were higher in patients treated with the vaccine-containing aluminium adjuvant. Previous studies on local adverse effects of these adjuvants have reported conflicting results. Can et al. reported that there is no difference between the rates of LR in patients treated with aluminium- or calcium-adsorbed allergen extracts⁴². However, in another previous study, it was shown that persistent subcutaneous nodules occurred in patients treated with aluminium-containing extracts⁴³. Unlike aluminium adjuvants, subcutaneous nodules due to calcium phosphate were not observed in this study. In contrast, Wütrich et al. found no subcutaneous nodules in patients treated with aluminium-containing extracts⁴⁴.

The main limitations of this study include its retrospective nature and single-centre study, which makes it difficult to make generalizations from the data presented. However, use of standard patient SCIT charts improved documentation and optimized data collection and analysis.

In conclusion, our study demonstrated that subcutaneous inhalant allergen immunotherapy was a safe treatment with a low risk to elicit SRs, in which no fatality was observed due to the SRs, during the 30 years. Considering the results presented in this study, we conclude that the LLR, aluminium-adsorbed extracts and recurrent LRs, but not asthma are important risk factors in possibly inducing SRs in patients who receive subcutaneous aeroallergen immunotherapy. Future prospective studies on side-effects with SCIT are necessary to confirm these associations.

Declaration of interest

The authors report no declarations of interest.

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