R. Asero

Detection of risk factors for systemic adverse reactions to SCIT with natural depot allergen extracts: a retrospective study

Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy

Key words

Allergen specific immunotherapy; subcutaneous immunotherapy; systemic reactions; airborne allergy; grass pollen; ragweed pollen.

Corresponding author
Riccardo Asero
Ambulatorio di Allergologia,
Clinica San Carlo
Via Ospedale 21
20037 Paderno Dugnano (MI), Italy
Phone: +39 02 990 38 470
Fax: +39 02 990 38 223
E-mail: r.asero@libero.it

Summary

Background. Some patients seem to show a particular propensity to experience systemic reactions (SR) when undergoing SCIT. This study looked at their features. Methods. 423 adults submitted to subcutaneous immunotherapy (SCIT) with 583 depot allergens extracts were studied. A "slow" build-up schedule was followed, and maintenance doses were given monthly. No mixtures of allergens were employed; multi-sensitized patients were treated with two extracts at the same time. IgE to pollen allergen components were measured. Patients experiencing several SR and those showing repeated large local reactions preventing up dosing were analyzed. Results. Altogether, 14% of patients experienced at least 2 SR to SCIT and further 13% repeated local reactions. All SR involved the skin. Eight treatments were stopped. No reactor was using beta-blockers. SR were not associated with pollen season, use of freshly prepared vials, administration of 2 allergens, or extract producer, nor were preceded by large local reactions. Reactors were younger than tolerant subjects ($p < 0.05$), and females were less frequently fully tolerant than males ($p < 0.001$). The multiple regression analysis showed that both ragweed and grass SCIT were significantly associated with adverse reactions ($p < 0.001$). Specific IgE to Amb a 1 or Phl p 1 did not differ statistically between reactors and tolerant subjects, whereas grass pollen-allergic reactors showed higher levels of IgE to Phl p 5. Intolerance did not depend on the number of primary sensitizations or on hypersensitivity to pollen pan-allergens. Conclusion. Young patients or women hypersensitive to grass and ragweed pollen seem at higher risk for SR during SCIT.

Introduction

Allergen-specific immunotherapy (SIT) is presently the only treatment able to change the natural history of respiratory allergic disease (1,2). Subcutaneous immunotherapy (SCIT) reduces rhino-conjunctivitis and asthma symptoms induced by allergen exposure, improves the quality of life, and may prevent the progression of the disease towards asthma (3). The only major concerns with allergen SCIT are adverse reactions. In previous studies, the frequency of systemic reactions induced by SCIT has been largely variable, depending on the allergen administered, treatment schedule, dose given, allergen standardization and clinical conditions before the start of the treatment (4-7). A recent survey carried out in Italian allergy centers concluded that SCIT is quite safe, as systemic reactions occurred only in 3.6% of patients and 0.15% of injections in more than 2000 courses (8) in accordance with other European studies (9-11). Nonetheless, a fraction of systemic reactions still remains and seems unavoidable and unpredictable. Particularly, in the clinical practice, along with adverse reactions that may occur in otherwise SCIT-tolerant patients possibly as the result of administration or of dosing errors, there are some patients showing a special, persisting intolerance to the treatment characterized by repeated adverse reactions even at low doses. The present study

analyzed retrospectively the outcome of SCIT in a large number of patients with the aim to investigate the clinical features of this latter population.

METHODS

Patients

The study involved mainly adult patients with respiratory allergy submitted to SCIT according to ARIA and WHO recommendations (1,2) for at least 2 years during the last 8 years. A minimum of 2 years of treatment duration was chosen in order to exclude from the analysis all patients that dropped out due to poor compliance short after starting SCIT without experiencing any adverse events, as these patients would have altered the overall prevalence of adverse reactions in the population studied.
No patient included in the present study had undergone allergen immunotherapy before. Respiratory allergy was diagnosed in the presence of an unequivocal clinical history of seasonal and or perennial rhinitis with or without conjunctivitis and/or asthma associated with a positive reaction on skin prick tests (SPT) with one or more commercial extracts out of a large panel of seasonal and perennial airborne allergens (Allergopharma, Reinbeck, Germany). The panel tested included timothy, mugwort, short ragweed, pellitory, plantain, birch, olive and cypress pollen (all 50000 BU/ml), house dust mite (HDM), *Alternaria tenuis* (10000 BU/ml), cat and dog dander (both 50000 BU/ml). SPT were carried out and read at 15' following EAACI guidelines. Wheals exceeding 3 mm in mean diameter were considered positive. All asthmatic patients prescribed allergen specific immunotherapy had a controlled disease at the start of SCIT and throughout the whole treatment period; further, no patient was using beta blockers during SCIT course.
Four-hundred-twenty-three patients with respiratory allergy (M/F 207/216; mean age 39.6 years, range 12-78 years) entered the study.

In-vitro diagnostics

The measurement of IgE specific both for markers of primary sensitization (rPhl p 1, rPhl p 5, rArt v 1, rAmb a 1, rPar j2, rBet v 1, rOle e 1, and rCup a 1) and for markers of sensitization to cross-reacting pollen pan-allergens (rPhl p 7 for polcalcin, and rPhl p 12 for profilin) has become available during the last 5 years in our Clinic. Patients showing skin reactivity to > 3 seasonal allergen sources (12) and willing to undergo allergen specific immunotherapy underwent these in-vitro tests in order to decide the most correct treatment(s). In case of IgE reactivity to multiple allergens the SCIT treatments were chosen on the basis of both clinical severity of symptoms and correspondence between positive allergen sources and seasonality of symptoms. Specific IgE were also measured in some patients showing few sensitizations on SPT, particularly in those with late summer symptoms hypersensitive to both ragweed and mugwort on SPT in order to discriminate between co-sensitization to and co-recognition of these two allergen sources (13). Specific IgE were measured by ImmunoCAP EIA (ThermoFisher Scientific, Uppsala, Sweden) following producer's recommendations and were expressed as kUA/L. Values < 0.35 kUA/L were considered negative.

Subcutaneous immunotherapy

All patients were treated with extracts of natural unmodified allergens in depot formulation (adsorbed on aluminum hydroxide or calcium phosphate). Standardized commercial allergen extracts from the following producers were used: Allergopharma, Reinbeck, Germany; Stallergenes, Anthony, France; Lofarma Allergeni, Milan, Italy; Hal Allergy, Leiden, The Netherlands; ALK, Horsholm, Denmark; Abellò, Madrid, Spain. Treatments and allergens given are summarized in **table 1**.
During the build-up phase, weekly injections were administered with the aim to reach the maximum tolerated dose (the so-called "optimal dose") within the upper limit recommended by the producer. Maintenance doses were given on a monthly basis. In pollen-allergic patients maintenance doses were reduced (14) by 50% during the pollen season of this geographical area (from mid-February to mid-April for cypress; from the beginning of March to mid-May for birch; from the end of April to the end of June for both Grass and Parietaria; and from mid-August to the end of September for both ragweed and mugwort). The dosage was properly reduced also in case of systemic adverse reactions. No patient did pre-medication before SCIT injections. After each injection, patients were kept under medical surveillance for 30 min. All data, including allergen extract dosage, local and systemic reactions were recorded. The same physician (R.A.) gave all shots and was also responsible for the treatment of all SCIT-induced adverse reactions. Patients allergic to several allergen sources and requiring more than one SCIT were treated with two distinct extracts who were administered one per arm at the same time. Allergen mixtures of non-homologous allergen sources were not employed for the treatment: the only mixtures used were grass pollen mix, a birch-hazel-alder pollen mix, and a mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. All patients gave an informed written consent before the start of treatment. Since the study was retrospective and based on routine clinical activity, a formal approval by the local Ethical Committee was not required. The internal Review Board approved the study.

Table 1 *- SCIT courses, allergen extracts used, and producers.*

	Total	Allergopharma	Abellò	ALK	Lofarma	Stallergenes	Hal
Total SCIT	583	403	17	21	32	100	10
Grass	143	99	3	7	19	9	6
Ragweed	270	175	8	3	6	78	0
Birch	80	67	1	6	1	4	1
Mugwort	13	11	0	0	0	2	0
Pellitory	15	10	0	0	5	0	0
Cypress	4	0	0	1	0	3	0
HDM	38	26	3	3	1	3	2
Alternaria	8	8	0	0	0	0	0
Cat	9	7	1	1	0	0	0
Dog	3	0	1	0	0	1	1

Grading of adverse reactions and patients classification

Both immediate (occurring within 30 min) and delayed (occurring after 30 min) systemic adverse reactions, were graded following the recent World Allergy Organization Subcutaneous Systemic Reactions Grading System (15). Briefly, Grade 1 includes symptoms/signs of one organ system (either cutaneous, upper respiratory, or conjunctival); Grade 2 includes either symptoms/signs of more than one organ system or lower respiratory, or gastrointestinal, or uterine cramps; Grade 3 includes asthma not responding to inhaled bronchodilator or laryngeal, uvular, or tongue angioedema; Grade 4 includes respiratory failure or hypotension with or without loss of consciousness; Grade 5 corresponds to death. Only patients experiencing more than one systemic reaction during the SCIT course were considered in this study. In some cases, SCIT had to be withdrawn due to repeated systemic reactions. The occurrence of repeated, severe large local reactions that prevented the up dosing of the SCIT throughout the whole treatment course was recorded as well.

Statistics

Means were compared non-parametrically by the Mann-Whitney U-test. Proportions were compared by the chi-square test with Yates' correction. Multiple stepwise logistic regression was applied to evaluate possible risk factors for systemic SCIT-induced reactions. Adjusted odds ratio (OR) and its 95% confidence interval (95% CI) were calculated. STATA 12.1 (StataCorp LP, College Station, Texas, USA) was used for this analysis. Probability values less than 5% were considered significant.

RESULTS

General findings

583 SCIT treatments were administered to the 423 patients included (i.e., 160 patients underwent SCIT with two distinct allergen sources at the same time). Allergens administered, extract producers, as well as standardization and major allergen concentration of the extracts are shown in **tables 1** and **2**. Altogether, 60/423 (14%) patients experienced at least 2 systemic adverse reactions to SCIT; 29 patients had Grade 1 reactions only, 18 Grade 2 reactions only, 12 both Grade 1 and Grade 2 reactions, and 1 patient experienced Grade 1, 2 and 4 reactions. Most systemic reactions were characterized by urticaria/angioedema only (Grade 1 reaction after WAO classification); in some cases, skin symptoms were associated with slight rhinitis or asthma (Grade 2 reactions). Both Grade 1 and 2 reactions were quite easily controlled by the use of injection antihistamines and short-acting beta-agonists. No cases of severe asthma occurred. One patient experienced one episode of hypotension associated with skin symptoms that responded promptly to epinephrine (Grade 4). The severity and/or recurrence of systemic adverse reactions led to stop the treatment in 8 cases. Adverse reactions did not occur preferentially during the pollen season, were not associated with the use of freshly changed vials or with new batches of allergen, and were not preceded by large local reactions in most cases. Further 54 patients (13%) experienced repeated large local reactions upon SCIT administration that, though not compromising efficacy, prevented the up dosing throughout the whole therapy course of 2-4 years. Altogether 309/423 patients did

Table 2 *- Standardization and major allergen concentration (if available) of the maintenance vial of the commercial extracts for SCIT used in study patients.*

	Allergopharma (Novo Helisen Depot)	Abellò (Pangramin)	ALK (Alutard SQ)	Lofarma (AlOH Retard)	Stallergenes (Phostal)	HAL Allergy (DepotHAL)
Grass	5000 UT/ml	1000 STU/ml	100000 USQ/ml	10000 U/ml	10 IR/ml	20000 AU/ml
(Phl p 5 μg/ml)	(n.a.)	(2.5)	(20.2)	(n.a.)	(0.7)	(n.a.)
Ragweed	2500 PNU/ml	1000 STU/ml	100000 USQ/ml	10000 U/ml	10 IR/ml	-
(Amb a 1 μg/ml)	(n.a.)	(9.0)	(n.a.)	(n.a.)	(10.0)	
Birch	5000 UT/ml	1000 STU/ml	100000 USQ/ml	10000 U/ml	10 IR/ml	20000 AU/ml
(Bet v 1 μg/ml)	(20.0)[1]	(22.5)	(12.3)	(n.a.)	(5.0)	(n.a.)
Mugwort	5000 UT/ml	-	-	-	10 IR/ml	-
(Art v 1 μg/ml)	(n.a.)				(n.a.)	
Pellitory	5000 UT/ml	-	-	10000 U/ml	-	-
(Par j 1 μg/ml)	(n.a.)			(n.a.)		
Cypress	-	-	100000 USQ/ml	-	10 IR/ml	-
(Jun a 1 μg/ml)			(n.a.)		(10.0)	
HDM	5000 UT/ml	1000 STU/ml	100000 USQ/ml	10000 U/ml	10 IR/ml	20000 AU/ml
(Der p 1 μg/m)	(n.a.)	(4.0)	(9.8)	(n.a.)	(2.0)	(n.a.)
(Der p 2 μ/ml)	(n.a.)	(2.0)	(0.7)	(n.a.)	(0.4)	(n.a.)
Alternaria	2500 PNU/ml	-	-	-	-	-
(Alt a 1 μg/ml)	(n.a.)					
Cat	2500 PNU/ml	1000 STU/ml	100000 USQ/ml	-	-	-
(Fel d 1 μg/ml)	(n.a.)	(2.0)	(14.6)			
Dog	-	1000 STU/ml	-	-	10 IR/ml	20000 AU/ml
(Can f 1 μg/ml)		(n.a.)			(2.0)	(n.a.)

n.a. = information not available. [1] = personal communication.

not experience systemic reactions nor repeated local reactions and reached the scheduled recommended doses.

The age analysis showed that patients experiencing systemic adverse reactions were significantly younger than those who did not (mean age 35.4 years [range 13-70] vs 40.2 years [12-78], respectively; $p < 0.05$). Such difference increased if patients who never experienced systemic reactions were divided into local reactors (mean age 37.3 years [range 13-75]; p = NS vs SCIT reactors) and fully tolerant subjects (mean age 40.8 years [range 12-78]; $p < 0.01$ vs SCIT reactors).

The gender analysis demonstrated that male patients were more frequently fully tolerant to SCIT than female patients (170/207 [82%] vs 138/ 216 [64%], respectively; $p < 0.001$), although this was due more to a lower prevalence of local reactions (13/207 [6%] vs 41/216 [20%], respectively; $p < 0.001$) than to a difference of systemic reactions (24/207 [12%] vs 36/216 [17%], respectively; p = NS).

The effect of sex and age was further investigated by multiple regression analysis, which confirmed that both younger age and female sex were associated with adverse reactions induced by SCIT ($p < 0.001$).

Looking at the possible link between systemic reactions and the number of SCIT administered it was found that patients treated with one or two extracts did not show any differences (43/263 [16%] vs 17/160 [11%], respectively; p = NS).

Table 3 shows SCIT tolerance in the whole study group. There was a marked prevalence of SCIT treatments with ragweed and grass pollen, which strictly reflected the frequencies of airborne allergies in this geographic area. Grass and ragweed were also the two allergens that caused most cases of adverse reactions as a whole and were characterized by the highest frequencies of adverse reaction. The multiple regression analysis showed that both ragweed and grass SCIT (adjusted by age and gender) were significantly associated with adverse reactions (OR 3.6, CI 95%

Table 3 *- Tolerance of allergen specific immunotherapy administered to the study population.*

	Total	Tolerated	Local reactions	Systemic reactions
Total SCIT	583	449 (77%)	58 (10%)	77 (13%)
Grass	143	101 (70%)	16 (11%)	26 (18%)[1]
Ragweed	270	197 (72%)	35 (13%)	38 (14%)[1]
Birch	80	70 (88%)	4 (5%)	6 (8%)
Mugwort	13	11 (85%)	0 (0%)	2 (15%)
Pellitory	15	12 (80%)	1 (7%)	2 (13%)
Cypress	4	4 (100%)	0 (0%)	0 (0%)
HDM	38	36 (93%)	1 (3%)	1 (3%)
Alternaria	8	8 (100%)	0 (0%)	0 (0%)
Cat	9	7 (78%)	1 (11%)	1 (11%)
Dog	3	2 (66%)	0 (0%)	1 (33%)

P < 0.01 for grass + ragweed vs all other treatments.

Table 4 *- Mean maximum tolerated doses of SCIT.*

	Tolerant	Local reactions	Systemic reactions
Ragweed (n = 270)	0.76 [0.4 - 1]	0.41 [0.1 - 0.75]	0.26 [0.02 - 0.35][1]
Grass (n = 143)	0.7 [0.3 - 1]	0.3 [0.05 - 1]	0.24 [0.02 - 0.7][1]
Mugwort (n = 13)	0.78 [0.6 - 1]		0.08 [0.02 - 0.15][1]
Pellitory (n = 15)	0.8 [0.3 - 1]	0.05	0.12 [0.05 - 0.2][1]
Birch (n = 807)	0.79 [0.25 - 1]	0.13 [0.05 - 0.2]	0.38 [0.08 - 0.7][1]
HDM (n = 38)	0.8 [0.5 - 1]		0.3[1]

Doses are expressed as ml of final vial.

[1]p < 0.001 vs tolerant patients.

2.0-6.4; p < 0.001 for ragweed) (OR 3.1, CI 95% 1.7-5.8; p < 0.001 for grass). In contrast, perennial airborne allergens other than animal dander (i.e., house dust mite and *Alternaria tenuis*) were very rarely involved in adverse reactions.

The 8 patients who stopped the treatment due to severe and repeated systemic adverse reactions were being treated with 12 extracts: grass (n = 6), ragweed (n = 2), pellitory (n = 2), birch and mite (n = 1 each), although, notably, both pellitory and the mite treatments were being given in association with grass pollen SCIT. In one patient treated with two extracts, ragweed SCIT was withdrawn due to repeated systemic adverse reactions while grass pollen SCIT was continued without any further problem.

Not surprisingly, the mean maximum tolerated doses of SCIT were significantly lower in patients who experienced systemic adverse reactions than in tolerant patients (p < 0.001 in all cases; **table 4**).

In order to detect possible differences between allergen extracts from different producers, the adverse reactions induced by SCIT with ragweed and grass pollen extract were re-analyzed based on the commercial extract used for the treatment but the statistical analysis did not show any difference in the prevalence of systemic adverse reactions between extracts from different producers. Further, the analysis of the SCITs carried out using the extracts from the most frequently employed producer (Allergopharma) confirmed the significant prevalence of seasonal allergens as a cause of systemic adverse reactions (systemic reactions: p < 0.025 for seasonal vs perennial allergens).

Specific IgE measurements

The possible association between specific IgE levels and adverse reactions upon SCIT administration was investigated for grass and ragweed pollen, the two allergens inducing the majority of systemic adverse reactions.

a. Ragweed pollen SCIT

IgE measurements were available for 65 patients. Baseline Amb a 1-specific IgE levels ranged between 3.9 and > 100 kU/L (median 42.5 kU/L), and did not show any difference between patients who experienced systemic reactions upon SCIT administration (n = 5; median 58.9 kU/L, range 6.1-94.1), those who experienced repeated local reactions (n = 7; median 39.0 kU/L, range 7.1 - 100), and those who tolerated the treatment well (n = 53; median 41.6 kU/L, range 3.92 - 100). Patients with and without a history of SCIT-induced systemic reactions did not differ in the mean number of primary sensitizations to allergen sources other than ragweed, nor in the prevalence of sensitization to any specific allergen source other than ragweed (data not shown). Further, SCIT-induced systemic adverse reactions were not influenced by the presence or absence hypersensitivity to the pollen pan-allergens, profilin and/or polcalcin.

b. Grass pollen SCIT

IgE measurements were available for 48 patients submitted to SCIT with grass pollen extract. Baseline IgE levels ranged between 2.5 and > 100 kU/L for Phl p 1 and 0 and > 100 kU/L for Phl p 5, respectively. Two out of the 9 patients who experienced systemic reactions had to stop SCIT due to their severity. The levels of IgE specific for Phl p 1 did not statistically differ between patients with a history of systemic reactions (n = 9; median 40.0 kU/L, range 9.1 - 94.8), local reactions (n = 6; median 25.8 kU/L; range 14.3 - 44.8), or good tolerance to the treatment (median 19.3 kU/L; range 2.5 - 100). In contrast, IgE specific for Phl p 5 were higher in subjects with a history of systemic reaction to SCIT (median 42.4 kU/L; range 14.6 - 100), than in those with a history of local reactions (median 28.4 kU/L; range 6.04 - 67.4), or those who tolerated SCIT well (median 8.7 kU/L; range 0 - 100). The difference was statistically significant ($p < 0.05$). Patients with and without a history of SCIT-induced systemic reactions did not differ in the mean number of primary sensitizations to allergen sources other than grass pollen, nor in the prevalence of sensitization to any specific pollen source other than grass pollen. Finally, grass pollen SCIT-induced adverse reactions were not influenced by co-recognition of the pollen pan-allergens, profilin and/or polcalcin.

DISCUSSION

Systemic reactions are considered to a certain extent an unavoidable risk associated with SCIT (7). Specific risk factors associated with systemic reactions include poor asthma control, concomitant medication (particularly beta-blockers), lack of dose adjustment during the pollen season, type of build-up protocol, and both administration and dosing errors (16). In the clinical practice, some patients seem to show an unexplainable propensity to react repeatedly and severely to SCIT in the absence of any of the risk factors summarized above. A second group of patients shows large local reactions even at low doses that prevent up dosing of the treatment; these patients also would probably experience systemic reactions if higher doses were given. Finally, the majority of patients submitted to SCIT experience slight local reactions, more rarely mild urticaria or asthma episodes, in most cases during the build-up phase, but eventually tolerate high doses of allergen extract for a long time without further problems. The present retrospective study tried to better characterize the clinical features of the patients belonging to the former group in order to detect risk factors for systemic reactions to SCIT. Notably, none of the patients with systemic reactions had severe asthma attacks following the shots; this is in keeping with the fact that no patient was taking beta-blocking agents, showed a poor asthma control, or was given high doses of allergen during the pollen season, all conditions that have been associated with respiratory adverse reactions. The analysis of our data ruled out some potential risk factors such as the number of extracts administered at the same time, the producer of the allergen extract, the number of baseline primary sensitizations to different allergen sources, hypersensitivity to the pollen pan-allergens profilin and polcalcin and, importantly, also the level of IgE specific for the major allergen of the extract administered (Amb a 1 and Phl p 1 for ragweed and grass pollen, respectively). However, interestingly, patients with a history of systemic and local reactions to grass pollen SCIT showed significantly higher levels of IgE to Phl p 5, another major allergen, than tolerant subjects. Previous studies found that a high degree of allergen sensitivity represents a risk factor for systemic adverse reactions (17-19). It is therefore possible that in the case of grass pollen allergy, IgE to allergens other than Phl p 1 play a role in increasing patients' reactivity to the treatment. In this study only IgE to Phl p 1 and Phl p 5 were measured; it cannot be excluded that IgE reactivity to one of the other currently available specific grass pollen allergens (i.e.; Phl p 2, Phl p 4, Phl p 6 or Phl p 11) may be also a risk factor for SCIT intolerance. In effect, studies carried out in children showed that the IgE response to grass pollen develops from Phl p 1 and only in a subsequent stage spreads to other allergens (20). It is therefore probable that high levels of IgE to allergens other than Phl p 1 are a marker of a heavier immune response to this allergen source. Further, allergen specific nasal/ocular provocations, along with quantitative measurement of SPT, would have theoretically provided two alternative means to assess a hyper-reactive state to be plotted against SCIT tolerance/intolerance but, unfortunately, such measurements were not carried out.

In this study, female gender was associated with a worse tolerance of SCIT, and systemic adverse reactions occurred more

frequently in younger patients as well as in subjects submitted to SCIT with seasonal allergens, particularly ragweed and grass. The lower tolerance to SCIT by female patients is in keeping with a number of other clinical conditions of allergological interest characterized by mast cell degranulation where a clear female prevalence can be observed, including chronic spontaneous urticaria, food allergy, respiratory allergy, and hypersensitivity to non-steroidal anti-inflammatory drugs (21-25). The higher rate of reactivity to pollen allergens (particularly grass and ragweed) than to perennial allergens is a novel finding and is not easy to explain. The possibility that commercial extracts of perennial allergens for SCIT may contain a relatively lower concentration of allergen proteins or of major allergens seems unlikely as each producer adopts the same standardization procedures in-vivo and in-vitro for all the allergens. Further, hypersensitive patients show equally elevated specific IgE levels for either seasonal or perennial allergens. Altogether, one gets the impression that grass and ragweed pollen allergens may possess an intrinsically higher ability to induce histamine release from mast cells and basophils of hypersensitive patients than allergens from house dust mite or molds although, clearly, further studies are needed to confirm this hypothesis.

In conclusion, young patients, and women hypersensitive to grass and ragweed pollen seem subsets at higher risk for systemic adverse reactions during SCIT. In grass-allergic patients, IgE to allergens other than Phl p 1 seem one further risk factor for SCIT adverse reactions.

References

1. Bousquet J, Lockey RF, Malling HJ, eds. WHO position paper allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy. 1998;(Suppl. 44):1-42.
2. Bousquet J, Van de Cauwenberge P, eds. Allergic Rhinitis and its Impact on Asthma (ARIA) WHO Position Paper. J Allergy Clin Immunol. 2001;108(Suppl. 5):S147-334.
3. Passalacqua G. Specific immunotherapy: beyond the clinical scores. Ann Allergy Asthma Immunol. 2011;107:401-4.
4. Hetal S, Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006;117:169-75.
5. Mellerup MT, Hahn GW, Poulsen LK, Malling HJ. Safety of allergen-specific immunotherapy. Relation between dosage and regimen, allergen extract, disease and systemic side effects during induction treatment. Clin Exp Allergy. 2000;30:1423-9.
6. Winther L, Malling HJ, Mosbech H. Allergen specific immunotherapy in birch and grass-pollen-allergic rhinitis. Side effects. Allergy. 2000;55:827-35.
7. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D. Systemic reactions to immunotherapy: influence of composition and manufacturer. Clin Exp Allergy. 2003;33:470-4.
8. Schiappoli M, Ridolo E, Senna GE, Alesina R, Antonicelli L, Asero R, et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy. 2009;39:1569-74.
9. Rank MA, Bernstein DI. Improving the safety of immunotherapy. J Allergy Clin Immunol Pract. 2014;2:131-5.
10. Nettis E, Giordano D, Pannofino A, Tursi A. Safety of inhalant allergen immunotherapy with mass units-standardized extracts. Clin Exp Allergy. 2002;32:1745-9.
11. Moreno C, Cuesta-Herranza J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy. 2004;34:527-31.
12. Ragusa RF, Passalacqua G, Gambardella R et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10 years' experience. J Invest Allergol Clin Immunol. 1997;7:151-4.
13. Villalta D, Asero R. Analysis of the allergenic profile of patients hypersensitive to pollen pan-allergens living in two distinct areas of Northern Italy. Eur Ann Allergy Clin Immunol. 2011;43:54-7.
14. Asero R, Bellotto E, Ghiani A, Aina R, Villalta D, Citterio S. Concomitant sensitization to ragweed and mugwort pollen: who is who in clinical allergy? Ann Allergy Asthma Immunol. 2014;113:307-13.
15. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling H-J, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61(Suppl 82):1-20.
16. Cox L, Larenas-Linnemann D, Lockey RF, et al. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125:569-74.
17. Rank MA, Bernstein DI. Improving the safety of immunotherapy. J Allergy Clin Immunol Pract. 2014;2:131-5.
18. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol. 1987;79:660-77.
19. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol. 1993;92:6-16.
20. Calabria CW, Stolfi A, Tankersley MS. The REPEAT study: recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions. Ann Allergy Asthma Immunol. 2011;106:49-53.
21. Matricardi P. Molecular profile clustering of IgE responses and potential implications for specific immunotherapy. Curr Opin Allergy Clin Immunol. 2013;13:438-45.
22. 2ohn LJ, Ahmed S, Anjum F, Kebab M, Mohammed N, Darwich H, Ibraheem N, Arifulla M, Sreedharan J. Prevalence of Allergies among University Students: A Study from Ajman, United Arab Emirates. Allergy. 2014.
23. Goksel O, Aydın O, Atasoy C, Akyar S, Demirel YS, Misirligil Z, Bavbek S. Hypersensitivity reactions to contrast media: prevalence, risk factors and the role of skin tests in diagnosis - a cross-sectional survey. Int Arch Allergy Immunol. 2011;155:297-305.
24. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol. 2010;35:869-73
25. Doña I, Blanca-López N, Torres MJ, Gómez F, Fernández J, Zambonino MA, Monteseirín FJ, Canto G, Blanca M, Cornejo-García JA. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014;69:438-44.