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Systemic Adverse Reaction to Specific Immunotherapy

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Abstract

Background: Allergen immunotherapy has been reported to be effective in reducing allergic symptoms and drug consumption in cases of respiratory allergy. However, some concerns still exist about the relative safety of allergen immunotherapy. This form of therapy has a potential risk of serious systemic reactions.

Objective: To evaluate the frequency of systemic reactions due to subcutaneous allergen immunotherapy in Iraq and to identify factors associated with increased risk of adverse systemic reaction.

Methods: From January 2000 to December 2008, we selected 693 patients with allergic rhinitis and asthma to receive subcutaneous specific immunotherapy. Prospective immunotherapy safety was evaluated by recording post-injection adverse effects. The adverse reaction observed during the administration of subcutaneous immunotherapy within a period of 9 years (2000-2008), was analyzed in this study.

Result: Data were obtained from 693 patients who received subcutaneous immunotherapy (SCIT). The mean number of skin tests positivity and number of injections were significantly higher in systemic reaction group compared to negative systemic reaction group. During the study period, a total of 39281 injections were administered to 693 patients. Of the 693 patients, 82 (11.8%) had systemic reaction, with an incidence of 2.1/1000 injection. Sixty nine of the 82 systemic reaction (84%) developed in the build up phase, versus 13 (16%) in the maintenance phase ($p<0.0001$), with respect to reaction time, 47 (57%) of the systemic reaction were immediate (within 30 minutes respect to reaction time), and 35 (43%) were delayed. There were higher significant influences of polysensitisation, age, asthma, combination of asthma and allergic rhinitis, type of allergen, and indoor allergens on the development of systemic adverse reactions to subcutaneous immunotherapy.

Conclusion: The present study suggests that SCIT was a safe treatment with a low risk to elicit severe systemic reaction, in which no fatality was observed. Furthermore, this study indicated that mold, HDM, asthma, presence of asthma and allergic rhinitis (AR), polysensitisation, and indoor allergens sensitization were a risk factors contributing to systemic reactions.

Keywords: Specific immunotherapy; Asthma; Allergic rhinitis; Risk factor; SCIT; Safety; Iraq; Tikrit

Introduction

Allergic diseases are commonly encountered medical condition that causes substantial morbidity and mortality worldwide. Avoidance of suspected allergens is a treatment for allergic conditions (allergic rhinosinusitis, asthma and allergic rhinitis) [1-3]. However, in many cases exposure to a particular allergen cannot be completely avoided. Available medical therapies are not always fully effective or well tolerated [4,5]. Allergen specific immunotherapy is treatment that an effective and well tolerated treatment approaches for allergic diseases [6]. Allergen specific immunotherapy is treatments that modifies the immunological response to allergens and induce a state of clinical tolerance [7]. Recent research has helped uncover the mechanisms by which allergen immunotherapy exerts its therapeutic effect paving the way for the development of safer more effective therapy for a wider of allergic diseases [8]. In consensus reports and meta-analyses, allergen immunotherapy has been reported to be effective in reducing allergic symptoms and drug consumption in cases of respiratory allergy due to pollens, mites, animal dander and moulds [9]. However, some concerns still exist about the relative safety of allergens immunotherapy. This form of therapy has a potential risk of serious systemic reactions, as it involves subcutaneous injection of allergen extracts to which the patients is sensitive [10]. Despite clear advances in the prevention of such reactions, varying rates of severs reactions have been reported since the introduction of standardized and more potent extracts [11-21].

The aim of this study was to evaluate the frequency of systemic reactions due to subcutaneous allergen immunotherapy in our country and to identify factors associated with increased risk of adverse systemic reaction.

Material and Methods

Patients

From January 2000 to December 2008, we selected 693 patients with allergic rhinitis and/ or asthma to receive subcutaneous specific immunotherapy according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines [22]. All injections during the induction and maintenance were administered at an immunotherapy unit by consultant physician. Prospective, immunotherapy safety was evaluated by recording post-injection adverse effects. Written informed

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consents were obtained from all patients (or their parents for children) before the initiation of immunotherapy and the guidelines were followed to monitor patients during allergen extract injection.

The adverse reaction observed during the administration of subcutaneous immunotherapy within a period of 9 years (2000-2008), was analyzed in this study. Demographic and clinical data and peak expiratory flow before and after injection were recorded by the investigators on a standardized form.

Immunotherapy schedule

Immunotherapy was given in term of conventional schedule. Conventional Immunotherapy build- up was typically given as injection per week until the maintenance dose was reached and it was given once monthly. Allergen vaccines were administered subcutaneously according to EAACI guidelines [23] after the patients had given their informed consent. The standard schedule is presented in Table 1. However, for patients with systemic reactions [if he developed systemic reactions following the first injection] the starting dose is reduced to 0.01 IR/ml. The stock solution was with 10 IR/ ml and to prepare starting dose solution, it was diluted as tenfold dilution for two times using phenol saline. Each allergen was in a separate vial.

Adverse reactions to immunotherapy

The adverse reactions to Immunotherapy were assessed according to EAACI classification [5] and systemic reaction was chosen as the main outcome measure. In order to neutralize any possible nocebo effect, grade 0 reactions (non specific symptoms) were excluded [12], local reactions were not considered. Reactions to immunotherapy were defined as immediate if they began within 20 minutes of injection; otherwise, they were termed late.

Asthma and allergic rhinitis diagnosis

The diagnosis of asthma and classification was performed by specialist physicians based on the National Heart Blood and Lung Institute/World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma [24]. Allergic rhinitis diagnosis was performed according to previously reported guidelines [25].

CONCENTRATION IR/ml	VOLUME INJECTED (ml)	WEEK
0.1	0.1	1
	0.2	2
	0.4	3
	0.8	4
1	0.1	5
	0.2	6
	0.4	7
	0.8	8
10	0.1	9
	0.2	10
	0.4	11
	0.6	12
	0.8	13
	0.8	14
	0.8	15
	0.8	16
	0.8	17
	0.8	18
	0.8	19
	0.8	20

A: INITIAL TREATMENT DOSES
For patients with systemic reactions, the treatment should start with 0.01IR/ml.
B: MAINTENANCE DOSES
The maintenance dose was with 0.8 ml of 10 IR/ml.

Table 1: Immunization protocol.

Lung function test

Computerized Spirometer (Autosphiror, Discom-14, Chest Corporation, and Japan) was used for measurement of FEV1 predicted percent of the patients at their enrollment in the study and when indicated according to studies design.

Skin prick test

The skin prick tests were performed for all patients and control and evaluated in accordance with European Academy of Allergy and Clinical Immunology subcommittee on allergy standardization and skin tests using standards allergen panel (Stallergen, France). The panel for skin test include: dust mite (Dermatophagoides farina, Dermatophagoides peteronyssinus), Aleternaria, Cadosprium, Penicillum mixture, Aspergillus mixture, Grasses mixture, Feather mixture, Dog hair, Horse hair, Cat fur, Fagacae, Oleaceae, Betulaceae, Plantain, Bermuda grass, Chenopodium and Mugworth. All tests were performed in the outpatient Asthma and Allergy Centre, Mosul by a physicianusing a commertial allergen extracts (Stallergen, France) and a lancet skin prick test device. A wheal diameter of 3 mm or more in excess of the negative control was considered as positive test result.

Allergen extracts for SCIT

Therapeutic vaccines containing allergen extracts were purchased from Stallergen, France. Both aqueous and glycenerated extracts were used to achieve a starting dose concentration of 0.1 IU/ml. The purchased stock solutions are at concentration of 0.1, 1 and 10 IU/ml. In standardized extracts the stock formulation was prepared by tenfold dilution. Separate vial was used for allergen extract to reduce proteolysis degradation. All extracts were stored at 8°C. Therapeutic vaccine varied with each individual patient based on specific allergen identified during testing. Moist patients received a variety of aeroallergen combination.

SCIT protocol

The treatment protocol is of two stage, the attack (build-up) and maintenance stages. The attack treatment with gradual increase in dose and concentration of vaccine content were carried weekly for a period of 20 weeks. The vaccine is injected by deep subcutaneous route in the posterior aspect of upper arm. The maintenance treatment dose given in a constant dose every 15 days and then every 4 or 6 weeks interval. The interval between two maintenance injections must not exceed 6 weeks. Local reaction size was measured 20 minutes after each injection. Observed large local reactions (more than 20 mm wheal size) mandated a repeat of the same dose on the next visit, while systemic allergic reactions (skin, respiratory, cardiovascular, and/or gastrointestinal) required a two-fold reduction in vaccine concentration. Maintenance dose was set in most cases at 0.5 of the stock standardized extracts.

Statistical analysis

Variables for analysis were selected from clinical variables based on results from another published studies and on clinical expert opinion [5,9,26]. Odd ratio was used to examine the relationship between each variable and systemic reaction to subcutaneous immunotherapy. The chi-square test was used to compare the clinical evaluation, skin prick test, and risk factor for development of systemic reaction. OR was calculated to determine the association between different risk factors and the development of systemic reaction. Discriminative power for risk relationship between allergens and probability of systemic reaction was assessed by a receiver operating characteristics (ROC) curve, which

plotted the sensitivity of systemic reaction detection against the false positive across a threshold of probabilities. Statistical analysis was performed with a software package (SPSS, version.17).

Results

Data were obtained from 693 patients who received SCIT. Their demographic characteristics and clinical features are shown in Table 2. Their age range from 6 to 75 years with a mean age of 33±15 year. There are no significant differences in age means between total patients group, patients group who developed systemic reactions and patients group without systemic reactions. Only 69 patients (10%) of the study population demonstrate positive skin prick test to monoallergen. The mean number for skin test positivity was significantly higher (P<0.0001) in systemic reaction group (7.6±3) compared to negative systemic reaction group (3.5±2).

The mean total number of injections was significantly higher (p<0.0001) in systemic reactions positive group (82.4±63.6) compared to systemic reactions negative group (55.2±41.8). Of the total subjects included in the study, 291 (42%) were male. Skin prick test was positive in 465 (67.1%) patient, while 411 (59.3%) patients were sensitive to HDM Table 3.

Variable	Mean (SD)	No of patients	(%)
Age range	6-75		
Age (year)			
Total mean age (SD) Mean age group with systemic reactions Mean age group without systemic reactions	33 (15) 34(15.1) 33 (14.8)		
Allergen positive (mean ± SD) Total systemic reactions positive systemic reactions negative	4 (2.5) 7.6 (3) 3.5 (2)		
No. injection Total systemic reactions positive systemic reactions negative	58.4 (45.7) 82.4 (63.6) 55.2 (41.8)		
Sensitization Mono Poly		69 624	10 90
Medical history Allergic rhinitis and/or Conjunctivitis and/or Asthma		596 409 235	86 59 34
Gender Male Female		291 402	42 58

Table 2: Demographic and clinical characteristic of patients.

Allergen	No positive skin test	Percent
Mold	465	67.1
HDM	411	59.3
Grass	168	24.2
Bermuda	162	20.4
Trees	135	18.2
Mugworth	120	17.3
Chenopod	99	14.3
Plantain	87	12.6
Feather	75	10.8
Cat	72	10.4
Dog	51	7.4
Horse	15	2.2

Table 3: Skin test sensitization.

During the study period, a total of 39281 injections were administered to 693 patients. Of the 693 patients, 82 (11.8%) had systemic reaction, with an incidence of 2.1/1000 injection (Table 4).

Sixty nine of the 82 systemic reaction (84%) developed in the build up phase, versus 13 (16%) in the maintenance phase (P<0.0001), with respect to reaction time, 47 (57%) of the systemic reaction were immediate, and 35 (43%) were delayed [29 (83%) of them were developed during the first hour after the injection]. The immediate systemic reactions were treated with parenterally injections of 200 mg hydrocortisone, subcutaneous epinephrine and chlorphenaramine maleate intramuscular injection. While the subjects with late systemic reactions did not need medical treatment.

None of the developed systemic reactions had life threatening reactions. Four (4.9%) of the systemic reactions were of grade 3 and 78 (95.1%) were of grade 2. For total patients, systemic reactions were common in subject with mould sensitization (68/82; 82.9%; 9.81% of total patients), followed by HDM (62/82; 75.6%; 8.95% of total patients) and trees (32/82; 39%; 4.62% of total patients) Table 5. With respect to allergen type grouping, of the 15 patients with positive skin test to horse allergen, 6 patients developed systemic reactions. In Plantain skin positive test (87 patients), 22 patients developed systemic reactions and in Mugworth group only 30 patients developed systemic reaction from 120 patients who are skin positive test. There was significant difference in SRs between mite and mould (P<0.0001) compared to other allergens.

A 24 risk factors (Table 6 & 7) were analyzed for their association with development of systemic adverse reactions following SCIT. There were a non significant influences of gender (OR=1, p=0.92), number of injections (OR=0.73, p=0.47), dog allergen (OR=1.4, p=0.37) and grass allergen (OR=1.5, p=0.09) on the development of systemic reactions (Table-5). However, there were a higher significant influences of polysensitization (OR=9.65, p=0.0001) and age (OR=4.2, p=0.03) on

Variable	Number or %
No. of total patients	693
systemic reactions	82
% systemic reactions / patients	11.8
% systemic reactions / injection	0.21

Table 4: frequency of systemic adverse reaction to SCIT.

	Total	Negative systemic reaction	Positive systemic reaction	Frequent type		
				Total patients receiving SCIT/693	Allergen skin test positivity [positive/ total number]	Total patients with ADR/82
HDM	411	349	62	8.95	15.1 [62/411]	75.6
Mold	465	397	68	9.81	14.6 [68/465]	82.9
Grass	168	142	26	3.75	15.5 [26/168]	31.7
Trees	135	103	32	4.62	23.7 [32/135]	39
Bermuda	162	136	26	3.75	16.0 [26/162]	31.7
Mugworth	120	90	30	4.33	25.0 [30/120]	36.6
Chenopod	99	75	24	3.46	24.2 [24/99]	29.3
Plantain	87	65	22	3.17	25.3 [22/87]	26.8
Feather	75	61	14	2.02	18.7 [14/75]	17.1
Cat	72	56	16	2.31	22.2 [16/72]	19.5
Dog	51	43	8	1.15	15.7 [8/51]	9.8
Horse	15	9	6	0.86	40 [6/15]	7.3

Table 5: Systemic reactions reaction in relation to allergen type.

the development of systemic reactions. Furthermore, asthmatic patients had greater tendency to have systemic reactions (OR=3.4, p=0.017) and this tendency was increased when patients were with combined asthma and allergic rhinitis (OR=4.2, p=0.003), Table 6.

In addition, allergen type was with a predictive value for development of systemic adverse reactions. SCIT with horse allergen was a high risk factor (OR=5.3, p=0.004)for development of systemic adverse reactions, followed by Trees (OR=3.5, p=0.0001), Mugworth (OR=3.3, p=0.0001), Plantain (OR=3.1, p=0.0001), Chenopodium (OR=2.9, p=0.0001), Mould (OR=2.6, p=0.0001), cat (OR=2.4, p=0.003), HDM (OR=2.3, p=0.0001), Bermuda (OR=2 , P=0.0007).

The systemic adverse reactions development was positively associated with patients sensitized to a specific combination of sensitization (data not shown). However, the number of patients in each group were small to give a validity for the statistical analysis. Patients who are sensitized to indoor allergens were more predominant to develop systemic reactions (OR=18.2, p=0.0000) that who are sensitized to outdoor allergens (OR=2.9, p=0.001). Furthermore, patients with polysensitisation to [HDM, Mold, Grass] were significantly [P=0.014] prone to develop systemic reaction to immunotherapy [OR= 3.04, 95% CI 1.3-7.11].

The ROC curve demonstrating the trade-off between sensitivity and specificity for systemic reaction that results from various probability threshold indicated that area under the curve was 0.657 (R^2=0.90, p=0.001), and the maximum discrimination point was a cut off probability of 0.0981. This cut off point produced the following values indicating diagnostic utility: sensitivity 0.83 (95% confidence interval 0.73-0.90); specificity, 0.64 (95% CI 61-68); positive predictive value, 0.67 (95% CI 0.63-0.71); negative predictive value, 0.94 (95% CI 0.89-0.96); positive likelihood ratio, 1.27 (95% CI 1.14-1.23) and negative likelihood ratio, 0.49 (95% CI 0.3-0.79).

Regression analysis indicated a significant corrections between frequency of systemic adverse reactions in patients receiving SCIT and specificity (r=0.99, p=0.000); and between frequency of systemic reactions and sensitivity (r=0.5, p=0.001), in relation to different allergens immunotherapy. This indicated a close relationship between the predicted probability of systemic reactions and the prevalence of such reactions observed within each allergen group.

Variable		No. of patients	Systemic reaction (%)	Odd ratio (95%CI)	P value
Age 0-14 15-75		 60 633	 3.3 12.6	4.2 (1-17.5)	**0.03**
Gender Female Male		 402 291	 11.9 11.7	1 (0.6-1.6)	0.92
Positive no. of allergen (skin prick test)		360 333	2.8 21.6	9.65(4.9-19.1)	**<0.0001**
No. of injections 1-20 21-		 66 627	 9.1 12.1	0.73(0.3-1.7)	0.47
Skin test to HDM	Negative positive	282 411	7.1 15.1	2.3(1.4-3.9)	**0.0001**
Mold	Negative Positive	228 465	6.1 14.6	2.6(1.4-4.8)	**0.0001**
Grass	Negative Positive	525 168	10.7 15.5	1.5(0.9-2.5)	0.09
Trees	Negative Positive	558 135	8.2 23.7	3.5(2.1-5.6)	**<0.0001**
Bermuda	Negative Positive	631 162	8.9 16.0	2(1.2-3.2)	**0.007**
Mugworth	Negative Positive	573 120	9.1 25.0	3.3(2-5.5)	**<0.0001**
Chenopod	Negative Positive	594 99	9.8 24.2	2.9(1.7-5)	**<0.0001**
Plantain	Negative Positive	606 87	10.0 25.3	3.1(1.8-5.3)	**<0.0001**
Feather	Negative Positive	618 75	11.0 18.7	1.8(1-3.5)	0.05
Cat	Negative Positive	621 72	10.6 22.2	2.4(1.3-4.4)	**0.003**
Dog	Negative Positive	642 51	11.5 15.7	1.4(0.6-3.2)	0.37
Horse	Negative Positive	678 15	11.2 40.0	5.3(1.8-15.2)	0.004

Table 6: Risk factor for systemic reaction during subcutaneous immunotherapy.

Allergen origin	Patients number		Patients No.	Percent	Odd ratio [95%CI]	P value
Indoor	580	Negative Positive	499 81	81.7 98.8	18.2 [2.5-132]	**0.0000**
Outdoor	443	Negative Positive	436 7	71.4 87.8	2.9 [1.5-5.7]	**0.001**

Table 7: Allergen origin as a risk factor for systemic reaction development to subcutaneous immunotherapy.

Discussion

The occurrence of adverse systemic reaction due to allergen immunotherapy remains a major problem for both patients and clinicians [11]. Despite many preventive measures against systemic reactions, there is no proven predictive factor the appearance, type and severity of reaction [11]. In the present study we could not find any influence of gender and number of injections upon the development of adverse systemic reactions.

Previous studies have documented several risk factors for systemic reactions to immunotherapy [27,28], but multiple sources of risk information may be variable geographically. Some reports have shown a higher frequency of adverse reactions in children than in adults [29,30]. However, in our study, there were more systemic reactions in patients over 14 years of age, a finding consistent with that reported by others [12]. The high frequency of systemic adverse reactions to immunotherapy may be due to immunological shift to the type 2 helper cell pattern and irreversible tissue lesions as a result of long disease duration in adults [12].

In reported studies [11,19,31], asthma is an important critical risk factor in the development of systemic and fatal reactions in immunotherapy. In the present study, all asthmatic patients were stable and under treatment. However, asthmatic had significantly higher rate of systemic reactions (OR=3.2, p=0.017) than those with allergic rhinitis alone (OR=0.29) and tendency to develop SRs was increased in patients with combined asthma and allergic rhinitis (OR=4.2, p=0.003). Our findings are consistent with the literature, in terms of increased incidence of SRs in asthmatic [11,19,31-35].

In a recent study, it was reported that most of the fatalities occurred in asthmatic with poor optimal control [20,36]. In contrast, to our findings other studies found no increase in the rate or severity of reactions in asthmatic patients [12,37]. According to our results and that reported by others [11], it should be suggested that even stable, well controlled asthmatic patients are prone to higher risk for systemic reactions. In a recent reported study [38], systemic reactions were predominant in patients with allergic rhinitis. However, Ragusa, et al. [39] reported higher incidence of SRs in patients with combined asthma and urticaria.

The variation in incidence of development of systemic reactions probably due to selection of patients for immunotherapy, the exclusion of uncontrolled asthmatic patients, and allergen type and source.

Regarding the type of allergen extract, Mould and HDM allergic patients, experienced systemic reactions more frequently compared to other inhalant allergens. However, the analysis of each inhalant allergen alone indicated that Grass, Feather and dog were not a risk factor for systemic reactions development during immunotherapy. Both Mould and HDM allergens systemic reactions development rates were significantly different (p<0.0001) from other inhalant allergens evaluated in this study. This finding was in consistent with some studies [19,32,40,41] and not with others [42]. Indoor allergens were a significant risk factor for development of systemic reactions to subcutaneous immunotherapy [OR=18.2, P<0.0001]. In addition, polysensitisation do influence the susceptibility of patients to develop systemic reactions following immunotherapy.

Although, this study indicated that polysensitisation to inhalant allergens may act as risk factor for systemic reaction development during immunotherapy. A specific pattern of combination was act as risk factor for systemic reactions development. From 9 patients with polysensitisation for 3 allergens, only one [11%] combination [HDM, Mold and Grass] may be considered as risk for development of systemic reactions during immunotherapy. In contrast, from 7 patients with polysensitisation for 4 allergens, 4 [57%] combinations may be considered as a risk factor for systemic reactions development. Furthermore, all combinations of 5 and 6 allergens were significant risk factors for systemic reactions development during immunotherapy. The polysensitisation may act as a risk factors by converting TH1/TH2 imbalance, in favor of TH2 and this may be basically due to increase in allergen load and type.

This study indicated that the development of systemic reactions was higher during the build-up-phase of immunotherapy. These observations confirm previous reports indicating that most systemic reactions occurred during the dose build-up-phase of immunotherapy [33,36,37]. However, Moreno et al, found similar rated of systemic reactions in both build-up dosing and maintenance phases of immunotherapy [32]. Furthermore, recently it was reported that most fatal reactions had developed with maintenance allergen doses [20].

The frequency of systemic reactions development was more as immediate reaction (57%). A finding consistent with that reported by others [9,35,41] and not agreed with results of others [11,19,42-44]. Although more than half of systemic reactions cases developed as immediate reactions, our results indicated an important aspect of development of 43% of systemic reactions were of late onsets. However, 83% of the assigned late reactions were developed in the period 25 minutes to 60 minutes after the injection. The most recent immunotherapy guidelines recommend a waiting period of 20-30 minutes after injection [5]. Although severe SRs usually appear within 30 minutes after injection, as we found in our study still there was high rate of patients can experience late onset systemic reactions. Thus we suggest that the observation of vaccinated patients should be extended more than 30 minutes in some patient settings, such as those with mold and/or HDM sensitization.

The frequency of development of SRs was 11.8% per patients, and this rate was lower to that reported by others [11,38,43,45]. However, our study finding SRs rate was higher than other reported studies [13,39,42,44].

The reported rate of systemic reactions per injection has been variable from 0.06% to 2.033% [9,11,13,19,31,32,35,39,42-47]. Our frequency of SRs was 0.21% and within the range reported by several studies. Furthermore our study indicated that development of SRs was lower in SCIT as compared to cluster and rash immunotherapy [9,11,35,48-51]. Thus the treatment with SCIT in asthma and allergic rhinitis were convenient for the patients even without premedication as this study indicated. Pretreatment with antihistamines has been proposed as an effective approach to reduce the side effects of immunotherapy [52]. There are controversial findings regarding the influence of antihistamine pretreatment on the occurrence of systemic allergic symptoms during allergen immunotherapy. Some studies indicated that pretreatment with antihistamine lead to a reduction in occurrence of systemic reactions following immunotherapy [52-57]. In contrast, other studies [58,59] observed no significant decrease of systemic reactions with the premedication use of antihistamines. It worth mentioning that antihistamine pretreatment does reduce systemic reactions without influencing the efficacy of immunotherapy [57].

In conclusion, the present study suggests that SCIT was a safe treatment with a low risk to elicit severe systemic reaction, in

which no fatality was observed. Furthermore, this study indicated that mold, HDM, asthma, presence of asthma and allergic rhinitis, polysensitisation, and indoor allergens sensitization were a risk factors contributing to systemic reactions.

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