Heliyon 9 (2023) e13100

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A single center retrospective study of systemic reactions' distribution and risk factors to subcutaneous immunotherapy with dust mite extract in patients with allergic rhinitis and/ or asthma

Xude Zhang [a], Jingjing Liu [a], Hui Chen [b], Beibei Guo [a], Fengxia Liu [a,*], Xijuan Wang [a,**]

[a] Department of Allergy, The First Affiliated Hospital of Weifang Medical University/ Weifang People's Hospital, Weifang, PR China
[b] Clinical Medicine College, Weifang Medical University, Weifang 261000, Shandong Province, China

ARTICLE INFO

Keywords:
Allergic rhinitis (AR)
Allergic asthma (AS)
Dust mite extract
Subcutaneous immunotherapy
Systemic reactions

ABSTRACT

Objective: To analyze various risk factors including causes that may lead to adverse reactions, especially systemic adverse reactions (SRs) , before and after mite allergen subcutaneous immunotherapy (SCIT), so as to provide real-world reference data for further improving the safety of mite allergen SCIT. **Methods**: The local adverse reactions (LRs) and SRs of 230 patients with allergic rhinitis and/or asthma who received SCIT in Weifang people's hospital were analyzed retrospectively. The data of patient characteristics, drug factors and environmental elements of adverse reactions were collected and statistically analyzed. **Results**: There were 28 cases (12.2%) of SRs in 230 patients. All the patients received a total of 7515 injections and 37 SRs (0.49%) were observed. 32.4% (12/37) of SRs could identify their external and subjective triggers. SRs patients had higher 2-year SCIT compliance than no-SRs patients ($p = 0.026$). The prevalence of SRs in SCIT patients with atopic dermatitis or simple allergic asthma are no statistical significance ($P = 0.111$). **Conclusion**: the incidence of SRs in this study is within an ideal range. Through professional patient education and pre injection risk factor assessment, Compliance is still well-controlled and guaranteed although SRs occurred.

1. Introduction

Dust mite, as a major aeroallergen widely existing all over the world, also ranks first in allergens causing allergic diseases in Weifang city [1]. Although allergen avoidance is the most effective treatment in theory, it is difficult to completely avoid exposure to mite allergens in real life. Allergen-specific immunotherapy(AIT) is the only specific and disease-modifying treatment for allergic conditions [2,3]. In the nearly century, starting with the SCIT of "hay fever", numerous patients with aeroallergen and even food allergens have experienced AIT with different purification methods and intake routes, including SCIT and the later SLIT, and SLIT-tablet treatment which may be widely used in the future.

* Corresponding author. Department of Allergy, Weifang People's Hospital, No. 151, Guangwen Street, Kuiwen District, Weifang 261041, Shandong Province, PR China.
** Corresponding author. Department of Allergy, Weifang People's Hospital, No. 151, Guangwen Street, Kuiwen District, Weifang 261041, Shandong Province, PR China
E-mail addresses: zhangxude@163.com (X. Zhang), wf_lfx@163.com (F. Liu), chnwxj@126.com (X. Wang).

https://doi.org/10.1016/j.heliyon.2023.e13100
Received 17 April 2022; Received in revised form 18 December 2022; Accepted 16 January 2023
Available online 20 January 2023

SCIT may cause some mild local adverse allergic reactions presented as redness or pruritus at the injection site but is also related to it an approximate 0.1%–4% risk of SRs per injection [4]. The SCIT safety issue has been greatly improved when the risk factors associated with allergen injections in patients with uncontrolled asthma has been recognized and therefore avoided [5]. Explore of other circumstances presumed to trigger adverse events according to the clinicians would be helpful in identifying important risk factors for injection-related SRs.

AIT injection in pollen sensitized patients during the pollen season may increases the risk of SRs [6,7]. A prospective survey of 1500 AR patients sensitized to a single allergen in the pediatric population showed that the incidence of SRs in AIT (SCIT and SLIT) was 1.53%, and the incidence of SRs in dust mite-allergic patients is lower than that in patients with pollen-sensitized [8]. There is conflicting and limited evidence in the current report about concomitant atopic dermatitis (AD) would increase or reduce the incidence of adverse reactions during SCIT in patients with allergic rhinitis and/or asthma [9,10]. Moreover, whether the high levels of serum specific IgE(sIgE) or occurrence of LRs will increase SRs risk is still controversial [11,12].

Routine pre injection medical history inquiry and pulmonary function monitoring before SCIT are essential to avoid different degrees of SRs and even fatal reaction. International consensus stated uncontrolled asthma, pregnancy, malignant tumors, serious autoimmune diseases and application of β-receptor blocker is regarded as the absolute or relative contraindication of SCIT [13], it is also used in clinical practice as a diagnosis and treatment guide in China [14]. Although the prior situation was effectively avoided before SCIT, unexpected SRs may still occur. Therefore, detailed risk factors analysis and induction of historical injection adverse reactions will be of great significance to further reduce SRs.

1.1. Patients

We retrospectively analysis 230 IgE-mediated disorders in allergen-sensitized subjects who underwent SCIT of allergen extract from house dust mites (Dermatophagoides farinae 50%, Dermatophagoides pteronyssinus, 50%)/Novo-Helisen-Depot (Allergopharma, Berlin, Germany) in the Allergy Department of Weifang People's Hospital from May 2013 to December 2018, including 135 males, 95 females. The primary endpoint was to observe the number and incidence of SRs in patients received SCIT of allergen extract. There were 135 patients under 18 years old when the immunotherapy initiated. This study is a retrospective and observational studies study in which the treatment process of patients is carried out according to the EAACI Allergen Immunotherapy User's Guide [15] and drug instruction, the dose was adjusted in the actual implementation. All participants were received at least one injection. Patients or guardians of children were informed and signed informed consent of SCIT. In addition, the study was approved by the Ethics Committee of the Ethics Committee of Weifang People's Hospital.

230 patients are 5–62 years old before treatment, children younger than 18 years old were defined as children and otherwise defined as adults in this study. Subjects were diagnosed with AR or AS according to the ARIA guidelines; they all had single allergen sensitization to Dust mites (Dermatophagoides pteronyssinus [*Dp*] and Dermatophagoides farina [*Df*]) that was confirmed by skin prick test (SPT) or serum sIgE detection before enrollment in the study. SPT results ≥"++" and sIgE≥1 grade were used as positive inclusion criteria. Other conditions, such as chronic obstructive pulmonary disease, pregnancy status, and previous exposure to dust mite-specific immunotherapy were excluded.

1.2. Treatment

Patients were recommended to receive conventional dose-increasing treatment and maintenance treatment according to the Summary of Product Labeling, characteristics and the dosage was titrated according to tolerability [16] #13). Treatment was initiated with the lowest dose of the weakest strength (strength 1), after the treatment start, regularly dose increased according to individuals' tolerability, until was reached the individual maximum dose or maximum dose of strength 3(1.0 ml). However, the dose may be increased only if the last dose was well tolerated. If not, the last dose would be repeated or reduced. While the interval between any two injections need to more than 7 days, an increase in the injection interval to up to 14 days. After the individual maximum tolerated dose was reached, the injection interval was gradually extended to 4–6 weeks for maintenance treatment.

Before each time of injection, the patient was free of acute symptoms of illness, such as allergic complaints or the cold; in particular, there must be no asthmatic complaints. The physicians and nurses regularly assess patients' physical examination(body temperature≤37.5 °C), peak expiratory flow(PEF **>** 80% of Predicted value). If these symptoms or abnormal index exists, the injection would be delayed.

After each injection, the patient needed to be medically supervised for at least 30 min and then evaluated by the physician. In individual cases, delayed local reactions may occur at the injection site, which should be considered to be a visible manifestation of the immune response. Patients also may rarely experience undesirable SRs several hours after an injection. All of these would be followed up and recorded immediately once if happens. The attending physicians assessed patients' LRs and SRs before the next injection and make a decision to take repeated dose or escalated dose. It is also necessary to record the general situation, clinical diagnosis, changes in symptoms and signs during immunotherapy, reactions after injection, specific conditions of adverse reactions and medication usage.

1.3. Classification and solutions of adverse reactions

The judgment of adverse reaction grading is based on the SCIT adverse reaction standard developed by World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System [17], SRs can be divided into 5 grades: grade 0 is asymptomatic or the symptoms are not related to immunotherapy; grade I is mild systemic reactions, including: local urticaria, rhinitis or

mild asthma; grade IIis manifested as Moderate systemic reactions, with slow-onset urticaria, more than 15 min, or with moderate asthma; grade III non-fatal severe systemic reactions, such as rapid onset of generalized urticaria, more than 15 min after injection In patients with severe asthma or angioedema, grade IV manifests as anaphylactic shock with rapid onset of skin itching, flushing, generalized urticaria, asthma attack, or hypotension. Adverse reaction can be divided into LRs and SRs according to the symptoms of the reaction. LRs in SCIT refer to any pruritus, redness, and swellings except pain located at the area of administration. In this study we only recorded the SRs and the larger LRs defined as the maximum diameter greater than 8 cm which might affect the patient's compliance. Thirty minutes is generally recognized as the critical time of immediate or delayed adverse reactions after SCIT injection. SRs and LRs involved in this study are rapid reactions. Local indurations and other discomfort symptoms after injection are not counted.

For LRs, the observation time after injection was extended to 45–60 min, temporary pharmacotherapy of cetirizine syrup and external application of ice bag at the injection site were routine given. The cutaneous presentations in grade I SRs may rapidly progress into more severe reaction, intramuscular injection of epinephrine (1:1000)and dexamethasone was administered in GradeI-III SRs, with the patients who developed chest tightness and suffocation after the injection of SCIT injection, inhaled corticosteroids (ICS) plus rapid, long-acting beta(2)-agonists (LABA) inhalation was added. The observation time was extended until the symptoms were relieved, and there was no stridor on lung auscultation. One case of delayed SRs was treated by local clinic and the symptoms were relieved, no LLRs and SRs progressed to a higher level of adverse reactions, no life-threatening GradeIVand fatal GradeVSRs occurred in this study.

1.4. Statistical methods

SPSS 26.0 software was used for statistical analysis of the data. Continuous data were described as P_{50} (P_{25}, P_{75}). Mann-Whitney *U* test was employed to compare the indexes between two groups. Categorical data were described as percentages. Chi-square test was used to analyze the rate or proportion between groups. Fisher's exact test would be used when the data did not meet the conditions of the chi-square test. $P < 0.05$ was considered statistically significant.

2. Results

2.1. Patients

From 2013 to 2018, a total of 7515 SCIT encounters in 230 double-mite sensitized patients were included in this study. There were 2(0.9%), 36 (15.7%), 66 (28.7%) and 126(54.8%) patients with AD, AS, AR and coexistence of multiple allergic diseases (Table 1). Among these subjects, the age distribution ranged from 5 to 62 years, with 153 (66.5%) children and 77 (33.5%) adults, with a median age of 12.0(P25:7.0, P75:28.3) years. Among the comorbid multiple immune diseases, 112 (48.7%) cases belonged to AR/AS (75 children and 37 adults), and 14 other types, including AR/AD, AR/Allergic conjunctivitis, AR/Urticaria, AR/AS/AD, AS/AD. AR/Allergic conjunctivitis and AR/Urticaria were not observed in children.

2.2. SCIT-related systemic reactions during administration

Of these administrations, 28 patients experienced 37 SCIT related SRs (0.49% or 4.9 per 1000 injections), only a single late-onset (beyond 30 min after injection) SRs was recorded in this study. When patients who experienced SCIT related SRs were compared with the no adverse reaction group, no difference was found between the groups in gender or age at the initiation of SCIT. It is noteworthy that the incidence of SRs in AD patients and simple AS during SCIT is significantly lower (1/37) than that in group beyond them. In terms of mean injection course (days), there was no significant difference between SRs group and no SRs group. The incidence of SRs is shown by demographic of patients in Table 2 and by age group in Table 3.

Among all SCIT-related SRs, 22 times (59.5%) were gradeI, 12 times (32.4%) were grade II, and 3 times (8.1%) were grade III, none of grade IVor gradeV SRs was observed. Cutaneous symptoms (73.0%) formed by generalized pruritus and urticarial within 30 min were the main manifestation of SRs. Secondly, SRs appears in the onset of lower respiratory tract symptoms (32.4%) manifested by

Table 1
Baseline demographic and clinical characteristics of patients.

Variable	Children (n = 153)	Adults (n = 77)	Overall (n = 230)	χ^2	*P*
Gender, n (%)				16.228	<0.001
Male	104(68.0%)	31(40.3%)	135(58.7%)		
Female	49(32.0%)	46(59.7%)	95(41.3%)		
Age, P50(P25, P75)	9.0(6.0,12.0)	35.0(27.5,44.5)	12.0(7.0,28.3)		<0.001[a]
Diagnosis, n (%)				2.533	0.469
AR	42(27.45%)	24(31.17%)	66(28.69%)		
AS	27(17.65%)	9(11.69%)	36(15.65%)		
AD	2(1.31%)	0(0.00%)	2(0.87%)		
Others	82(53.59%)	44(57.14)	126(54.78)		

[a] Represents MannWhitney *U* test.

Table 2
Demographic of patients with SCIT-related SRs and no SRs.

Demographic	Overall	Patients with SRs	Patients with no SRs	χ^2	*P*
Gender				0.994	0.319
Male	135	14	121		
Female	95	14	81		
Age				−0.898	0.369
P_{50} (P_{25},P_{75})	14.00 (5.00,16.00)	13.5 (7.50, 34.25)	12.00 (7.00,27.00)		
sIgE grade				−0.971	0.331
P_{50} (P_{25},P_{75})	6.00 (5.00,6.00)	5.00 (3.25,6.00)	4.00 (3.00,6.00)		
Treatment course (days),				−0.783	0.434
P_{50} (P_{25},P_{75})	1566.00 (1290.00,1786.00)	901.00 (740.75,1146.75)	841.00 (286.50,1153.00)		
Course of treatment				4.986	0.026
Above 2 years	136	22	114		
Below 2 years	94	6	88		
Diagnosis					0.111[a]
AD	14	1	13		
Simple AS	36	1	35		
other type	180	26	154		

[a] Represents Fisher's exact test.

Table 3
Symptoms of SCIT-related LLRs & SRs by age group.

	Children (n = 153) n (%)	Adults (n = 77) n (%)	Overall (n = 230) n (%)	χ2	P
Total Large local reactions	20(13.07) 3(1.96)	12(15.59) 1(1.30)	32(13.91) 4(1.74)	0.270	0.603 1.000a
Systemic reactions	17(11.11)	11(14.29)	28(12.17)	0.483	0.487
Systemic urticaria	13(8.50)	5(6.49)	18(7.83)	0.285	0.593
Respiratory and thoracic disorders					
cough	2(1.31)	3(3.90)	5(2.17)		0.337 a
chest tightness	3(1.96)	3(3.90)	6(2.61)		0.405 a
asthma	1(0.65)	1(1.30)	2(0.87)		0.619 a
nasal disorders					
stuffy nose	0	1(1.30)	1(0.43)		0.335 b
conjunctivitis	0	1(1.30)	1(0.43)		0.335 b

Denominator for % calculation was the total number of patients in each respective group from SAF. a represents Fisher's exact test.

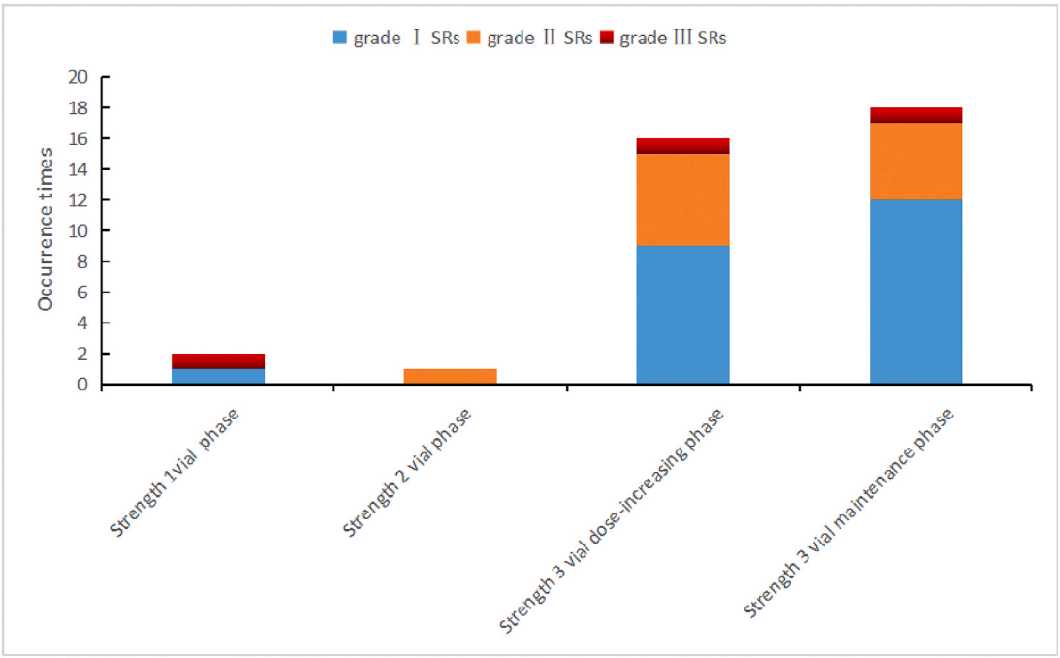

Fig. 1. Occurrence times of SRs in different injection phase.

chest tightness, cough and shortness of breath, gastrointestinal symptoms and allergic rhinitis with conjunctivitis occurred in 2 adult female patients respectively.

For the perspective of administration dose, the numbers of SRs in the Strength1-3 dose-increasing phase and Strength 3 maintenance phase were 2, 1, 16, and 18, respectively. Incidence of gradeI-II SRs in Strength 3, both dose-increasing phase and maintenance phase are higher than Strength 1–2(Fig. 1). In terms of time, we observed that SRs occurs in each month; it was less (1–2 times) in January, February, July, August and October, while the incidence in December was more prominent, for 8 times (Fig. 2).

We sorted out the relevant information about patients' daily activities and discomfort symptoms before and after SCIT in the data set, and observed some factors that may trigger SRs. Twelve events (32.4%) were screened out, among which 8 cases (21.6%) were caused by strenuous exercise, hot bath or eating sensitized food before or after injection, and 2 cases were caused by AR onset before injection, accounting for 5.4%. There was 1 case (2.7%) of SRs caused by irregular injection interval during treatment. Other SRs was arising by the patient's sensitivity to drugs and poor tolerance.

2.3. Compliance

Of the 230 patients who participated in the study, 59.1% (136) completed at least two years treatment. Case records and follow-up of patients showed there were three dominant reasons of terminating treatment: firstly, each patient must be administered in the clinic. The frequency of SCIT conflicts with the disposable time of patients (42.6%), especially school-age children; Secondly, economic factors mainly involve adult patients (28.7%), they switch AIT treatment regimen to inexpensive but frequently administered SLIT or SCLT without sustained release characteristic; The third cause attributed to the failure improvement of patient's self-reported symptoms (13.8%). Only 6.4% of the unexpected lower compliance was attributed to the concern of patients or their parents about local/systemic adverse reactions.

3. Discussion

Although there was rising trend of allergic diseases caused by airborne allergens in China, there are only a few dust mite extracts for use in SCIT at present, two of them are adsorbed to aluminum to standardize in standard quality units and retard the rate of systemic dispersal of the allergen, with the purpose of further improving the efficacy and reducing the incidence of SRs [18,19]. The efficacy and safety of SCIT are contradictory to some extent, sufficient effectiveness often represents a higher incidence of adverse reactions, nevertheless, without the reduction of SCIT compliance compared with SLIT [20,21]. Some subjective or objective events such as uncontrolled asthma, history of prior systemic reactions, high allergen season, accelerated injection course, dose error and so on are regarded as risk factors of SRs [4]. In this retrospective study, we found that the SRs incidence of SCIT with allergen extract from house dust mites is 0.49%, which is roughly equivalent to 0.48% reported by Zhang et al. [22] and 0.47% reported by Chen et al. with the same product [9]. We observed many demographics, clinical characteristics and patient behavior that may be listed as risk factors for SRs. It is worth noting that only 2 patients with SRs involved in this study terminated SCIT due to the occurrence in the Strength1, the remaining patients persisted at least two years of injection despite sustained one or more SRs. Notably, the majority of LLRs and roughly half of SRs occurred in the conventional up-dosing phase, which also shows that maintain treatment with the SCIT allergen extract tends to reduce the incidence of local adverse reactions [16] and SRs.

By taking two ways, the patients in SRs group have better 2-year compliance than those in no SR group in this study. On the one

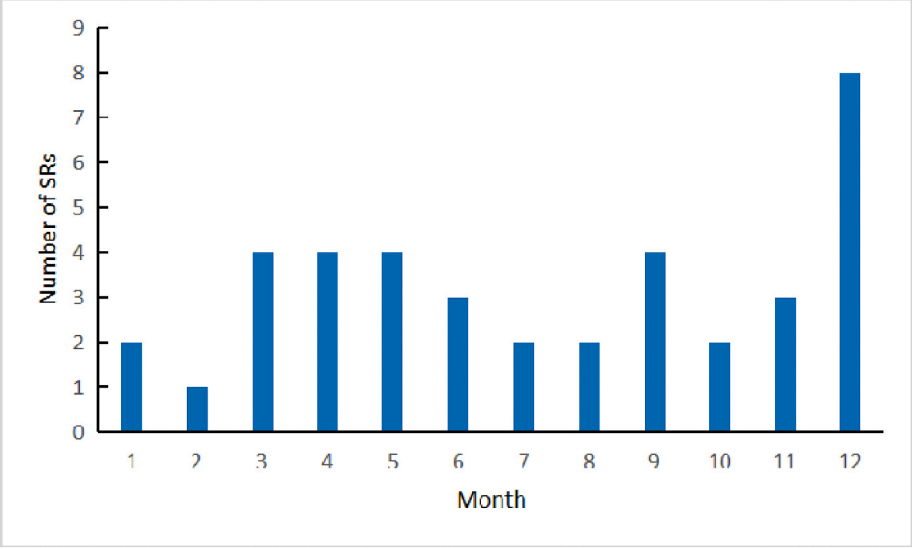

Fig. 2. Number of SRs occurrences in each month.

side, we improved patient education to patients with SR. Then they realize the occurrence of SRs just come from the immune response of immunotherapy. On the other side, pay more attention and prolong the supervised time in these patients after injections, solve the safety issues as soon as possible so that to strengthen their confidence and determination about SCIT. As a result, 22(78.6%) patients with SR completed at least two-years AIT eventually.

This study has not shown a causal relation between patient characteristics (gender, age) and the tendency of SRs. Up to now, there was limited evidence that aeroallergen-sIgE can be used alone or in combination with other factors as SRs predictors of AIT, one study on bee venom desensitization shows that low sIgE associated with severe SRs [23], there was also no significant difference in dust mite sIgE level between SRs group and no SRs group in our research. In addition to single AR, AR' comorbidities were included, patients suffer from other clinical indications [15] of SCIT such as single AS (15.6%) and with AD (6.1%) were also selected in this study. At present, there was conflicting evidence to show the exact efficacy of AIT in AD patients, or SCIT is currently not recommended as a general treatment option for AD [24], but it is an indisputable fact that AD and simple AS patients have low SRs rate(1/37) in this study. It is worth noting that the proportion of disease in this study does not represent the actual incidence rate. The high enrollment rate of AS may reflect AS patients' poor tolerance to disease, so they are preferred to choose SCIT which is usually described as etiological treatment.

In this study on the risk factors of SRs, we found that in addition to the above objective factors, the inductive behavior of patients before and after injection is an important trigger for the occurrence of adverse reactions, such as factors that accelerate local or systemic blood circulation within 12 h before and after injection, carsickness and fatigue on the way to the clinic and unplanned cluster buildup schedules [25]. Beyond these risk factors involved in the contraindications or precautions of the drug instructions, we found another situation that needs be emphasized: complications other than uncontrolled asthma before injection, such as onset of AR and AD attack caused by food.

In addition to the SRs-trigger we observed above, more than 2/3 of SRs still have no specific high-risk factors, and the suggestive detection of SRs beyond lung function test/PEF was still unclear. In clinical practice, there were rare reliable biomarkers for predicting the safety and accurately reflecting effectiveness of AIT [26,27]. Local reactions were poor predictors of local reactions with the next injection, thus, the evidence from Two large studies does not support a modification in dosing because of a LLRs, with the expectation of decreasing the likelihood of an SRs with the next injection [19,28]. In addition to the detection of lung function in clinical SCIT treatment, fractional exhaled nitric oxide(FENO) [29], as an indicator of airway eosinophilic inflammation, may be a potential and realistic predictable marker of SRs.

Intramuscular epinephrine is an internationally recognized first-aid management for anaphylaxis or acute severe allergic reactions [30], up to now, no epinephrine auto injector available in China, one follow-up Study shows that over 95% of SRs occur within 30 min after SCIT injection [31], instant symptom-relieving pharmacotherapy to minimize SRs before, during and after immunotherapy depends on the timely and correct diagnosis of clinicians. In this study, antiallergic drugs such as H1-antihistaminesin syrup form and/or LABA were used to treat SRs of grade I–III, for patients with SRs history and injection in the dose-increasing stage of Strength 3 were give H1 antihistamines before SCIT orally. These drugs can effectively control the symptoms and lay a foundation for further immunotherapy. There was still controversy regarding whether to adjust the injection dose after the occurrence of LLRs to reduce the risk of SRs [19]. In this study, there is no intersection and age group bias in patients between the occurrence of LLRs and SRs, but from the total number, especially the absolute value of SRs, it can be perceived that the incidence of adverse events in children is lower than adults, which may be related to the attention paid by these parents to the precautions before and after children's AIT injection, thus effectively avoiding some risk factors that may cause adverse reactions.

Dust mites generally exist as perennial allergens, but obviously their concentration or reproductive quantity also has seasonal regularity. Xiang et al. [32] collected indoor dust samples from Beijing dust mite sensitized patients and measured the content of main protein components of dust mite allergens. The results showed that the average concentration of house dust mites was significantly higher in winter, followed by autumn. Feng et al. [33]investigated the reproduction of indoor dust mites in northern China. They found that mites began to reproduce in March; the number of mites began to rise from April to May and reached the peak in September. In this study, we found that the highest incidence of SR in December, it may be caused by environment changes of north China. In winter, there is a higher concentration of mites indoor. In the middle of November, the weather gets cold, northern China begin to close the windows and use heaters, air indoor becomes poor-ventilation and dry. Most families use a humidifier to increase indoor temperature and humidity which are suitable for mite reproduction. The markedly increasing SRs from March to May and September can also be explained by the seasonality of mite allergens from the above reports. However, the spread of seasonal pollen allergy may be also one reason which lead to elevated SR, but this hypothesis needs to be evaluated in future study.

These were few limitations presented in this study. First, some data may be missing during retrospective data collection. Secondly, as the sample size of adults in the data set is smaller than that of children, there may be some deviation when analyzing adverse reaction differences between the two age groups.

In conclusion, the incidence of SRs in this study matching that reported in previous studies. We found that except for 1/3 SRs with clear risk factors which expected to be further reduced through patient education and pre injection evaluation by clinicians, most SRs are unpredictable, and new biomarkers and examination methods that can predict adverse reactions need to be developed. In addition, in this study, the compliance of SRs group is higher than that of no SRs group, which may suggest that SRs group has better curative effect. There was only 1/37 case of SRs in both AD patients and as patients, and its underlying molecular mechanism remains to be studied. The reproduction and increased concentration of indoor mite allergens are also a risk factor for SRs.

Author contribution statement

Zhang Xu-De: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Liu Jing-Jing; Chen Hui: Performed the experiments; Analyzed and interpreted the data.
Guo Bei-Bei: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Liu Feng-Xia; Wang Xi-Juan: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Funding statement

M.D. Feng-Xia Liu was supported by The Entrusted Program of Shandong ADR Monitoring Center [2021SDADRKY10].
Xu-De Zhang was supported by Scientific Research Program of Weifang Health Commission [WFWSJK-2021-225].

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] Z. Xu-De, G. Bei-Bei, W. Xi-Juan, L. Hai-Bo, Z. Li-Li, L. Feng-Xia, Serum IgE predicts difference of population and allergens in allergic diseases: data from Weifang city, China, Mediat. Inflamm. 2021 (2021), 6627087.
[2] C. Caffarelli, J. Cangemi, C. Mastrorilli, A. Giannetti, G. Ricci, Allergen-specific immunotherapy for inhalant allergens in children, Curr. Pediatr. Rev. 16 (2020) 129–139.
[3] R.S. Mueller, Update on allergen immunotherapy, Vet. Clin. North Am. Small Anim. Pract. 49 (2019) 1–7.
[4] M. Sanchez-Borges, D.I. Bernstein, C. Calabria, Subcutaneous immunotherapy safety: incidence per surveys and risk factors, Immunol. Allergy Clin. 40 (2020) 25–39.
[5] T.G. Epstein, G.M. Liss, K.M. Berendts, D.I. Bernstein, AAAAI/ACAAI subcutaneous immunotherapy surveillance study (2013-2017): fatalities, infections, delayed reactions, and use of epinephrine autoinjectors, J. Allergy Clin. Immunol. Pract. 7 (2019) 1996–2003 e1991.
[6] L. Cox, H. Nelson, R. Lockey, C. Calabria, T. Chacko, I. Finegold, M. Nelson, R. Weber, D.I. Bernstein, J. Blessing-Moore, et al., Allergen immunotherapy: a practice parameter third update, J. Allergy Clin. Immunol. 127 (2011) S1–S55.
[7] T.G. Epstein, G.M. Liss, K. Murphy-Berendts, D.I. Bernstein, AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? Ann. Allergy Asthma Immunol. 110 (2013) 274–278, 278 e271.
[8] P. Rodriguez Del Rio, C. Vidal, J. Just, A.I. Tabar, I. Sanchez-Machin, P. Eberle, J. Borja, P. Bubel, O. Pfaar, P. Demoly, et al., The European survey on adverse systemic reactions in allergen immunotherapy (EASSI): a paediatric assessment, Pediatr. Allergy Immunol. 28 (2017) 60–70.
[9] J. Chen, B. Li, Y. Zhao, Q. Zhang, L. Wan, J. Liu, X. Tian, G. Li, J. Zhou, L. Zhang, et al., A prospective multicenter study of systemic reactions in standardized specific immunotherapy for allergic rhinitis in China, Am. J. Rhinol. Allergy 28 (2014) e40–e44.
[10] Y. Yang, D. Ma, N. Huang, W. Li, Q. Jiang, Y. Wang, X. Wang, L. Yang, R. Zhu, Safety of house dust mite subcutaneous immunotherapy in preschool children with respiratory allergic diseases, Ital. J. Pediatr. 47 (2021) 101.
[11] P. Gur Cetinkaya, M. Kahveci, S. Esenboga, B. Karaatmaca, O. Soyer, B.E. Sekerel, A. Tuncer, U.M. Sahiner, Systemic and large local reactions during subcutaneous grass pollen immunotherapy in children, Pediatr. Allergy Immunol. 31 (2020) 643–650.
[12] H.T. Nacaroglu, S.B. Erdem, O. Sumer, S. Karaman, C.S. Unsal Karkiner, S. Asilsoy, I. Gunay, D. Can, Local and systemic reactions to subcutaneous allergen immunotherapy: ten years' experience in a pediatric clinic, Ann. Allergy Asthma Immunol. 116 (2016) 349–353.
[13] S.K. Wise, S.Y. Lin, E. Toskala, R.R. Orlandi, C.A. Akdis, J.A. Alt, A. Azar, F.M. Baroody, C. Bachert, G.W. Canonica, et al., International consensus statement on allergy and rhinology: allergic rhinitis, Int. Forum Allergy Rhinol 8 (2018) 108–352.
[14] Y. Bao, J. Chen, L. Cheng, Y. Guo, S. Hong, W. Kong, H. Lai, H. Li, H. Li, J. Li, et al., Chinese Guideline on allergen immunotherapy for allergic rhinitis, J. Thorac. Dis. 9 (2017) 4607–4650.
[15] M. Alvaro-Lozano, C.A. Akdis, M. Akdis, C. Alviani, E. Angier, S. Arasi, L. Arzt-Gradwohl, D. Barber, R. Bazire, O. Cavkaytar, et al., EAACI allergen immunotherapy user's guide, Pediatr. Allergy Immunol. 31 (Suppl 25) (2020) 1–101.
[16] L. Xiang, F. Liu, L. Zhi, W. Jiang, C. Liu, H. Xie, X. Zhou, Y. Sun, Y. Zheng, R. Zhu, et al., Safety of semi-depot house dust mite allergen extract in children and adolescents with allergic rhinitis and asthma, Immunotherapy 13 (2021) 227–239.
[17] L. Cox, D. Larenas-Linnemann, R.F. Lockey, G. Passalacqua, Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading System, J. Allergy Clin. Immunol. 125 (2010) 569–574, 574 e561-574 e567.
[18] Y. Bao, J. Chen, L. Cheng, Y. Guo, S. Hong, W. Kong, H. Lai, H. Li, J. Li, T. Li, et al., Chinese Guideline on allergen immunotherapy for allergic rhinitis, J. Thorac. Dis. 9 (2017) 4607–4650.
[19] H.S. Nelson, Allergy immunotherapy for inhalant allergens: strategies to minimize adverse reactions, Allergy Asthma Proc. 41 (2020) 38–44.
[20] D.X. Ji, J.R. Tan, H.W. Yu, [Efficacy, safety and compliance of immunotherapy in the treatment of allergic rhinitis: a Meta-analysis], Zhonghua er bi yan hou tou jing wai ke za zhi 54 (2019) 894–901.
[21] W. Liu, Q. Zeng, C. He, R. Chen, Y. Tang, S. Yan, X. Luo, R. Luo, Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis, Pediatr. Allergy Immunol. 32 (2021) 86–91.
[22] W. Zhang, Y. Deng, H. Tong, R. Xiang, S. Chen, Y. Kong, Z. Tao, Y. Xu, Adverse reactions to subcutaneous immunotherapy in patients with allergic rhinitis, a real-world study, Eur. Arch. Oto-Rhino-Laryngol. 278 (2021) 4353–4360.
[23] P. Korosec, K. Ziberna, M. Silar, M. Dezman, N. Celesnik Smodis, M. Rijavec, P. Kopac, R. Erzen, N. Lalek, N. Bajrovic, et al., Immunological and clinical factors associated with adverse systemic reactions during the build-up phase of honeybee venom immunotherapy, Clin. Exp. Allergy 45 (2015) 1579–1589.

[24] A. Wollenberg, J. Szepietowski, A. Taieb, J. Ring, Corrigendum: consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I, J. Eur. Acad. Dermatol. Venereol. 33 (2019) 1436.
[25] A.W. Winslow, J.C. Turbyville, J.W. Sublett, J.L. Sublett, S.J. Pollard, Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy, Ann. Allergy Asthma Immunol. 117 (2016) 542–545.
[26] C. Pitsios, Allergen immunotherapy: biomarkers and clinical outcome measures, J. Asthma Allergy 14 (2021) 141–148.
[27] S. Sani, R. Gupta, L. Fonacier, M. Aquino, Risk stratification of systemic reactions to subcutaneous immunotherapy: a retrospective study, Allergy Asthma Proc. 40 (2019) 338–342.
[28] C.W. Calabria, C.A. Coop, M.S. Tankersley, The LOCAL Study: local reactions do not predict local reactions in allergen immunotherapy, J. Allergy Clin. Immunol. 124 (2009) 739–744.
[29] L. Calciano, L. Portas, A.G. Corsico, M. Olivieri, P. Degan, M. Ferrari, A. Fois, A.M.F. Pasini, A. Pasini, M.E. Zanolin, et al., Biomarkers related to respiratory symptoms and lung function in adults with asthma, J. Breath Res. 12 (2018), 026012.
[30] M.C. Pflipsen, K.M. Vega Colon, Anaphylaxis: recognition and management, Am. Fam. Physician 102 (2020) 355–362.
[31] X. Dong, N. Huang, W. Li, L. Hu, X. Wang, Y. Wang, N. Xiang, G. Liu, R. Zhu, Systemic reactions to dust mite subcutaneous immunotherapy: a 3-year follow-up study, Allergy Asthma Immunol. Res. 8 (2016) 421–427.
[32] L. Xiang, Y. Fu, J. Wang, Q. Wang, [The correlation between the seasonal variation of house dust mite allergens exposure level in household and the level of asthma control in asthmatic children], Zhonghua Er Ke Za Zhi 52 (2014) 177–183.
[33] M. Feng, W. Sun, X. Cheng, Seasonal dynamics and distribution of house dust mites in China, Biosci. Trends 3 (2009) 210–215.