

Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine

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ABSTRACT

The use of epinephrine for anaphylaxis to subcutaneous allergen immunotherapy (SCIT) is the standard of care, but its use for mild systemic reactions (SRs) is somewhat controversial. The objective of this study is to determine the rate of SR to SCIT, the symptoms reported, and the response to intramuscular (i.m.) epinephrine over a 1 year period. This retrospective study was designed to evaluate SRs to SCIT to any combination of approximately 20 allergens (pollens, animal emanations, molds, and Hymenoptera) in 773 subjects representing 14,707 visits, receiving approximately 28,000 injections over 1 year. Nurses were instructed to administer epinephrine (1:1000 v/v) 0.2 mL i.m. for signs or symptoms of a SR. SRs were graded using the universal grading system proposed by the World Allergy Organization (WAO) Joint Task Force for Grading SR to Immunotherapy. Thirty-one patients (4%) had 32 SRs, 22 (71%) female, average age 40 yr. Nineteen (61%) had a history of asthma; 7 (22.6%) had a history of a previous SR. SRs were reported on average 24 minutes after injection. Symptoms included: generalized pruritus, 34.4%; upper airway pruritus, 28.1%; cough, 25.0%; shortness of breath, 21.9%. Fourteen SRs were classified as Grade 1, thirteen Grade 2, two Grade 3, and three Grade 4. No Grade 5 or late phase reactions were reported. 29 (90.6%) reactions were treated with epinephrine, 27 (84.4%) glucocorticosteroid, and 30 (93.8%) H1 antihistamine. SRs occurred in 4% of patients receiving SCIT and all who received early intervention with epinephrine responded successfully. The WAO Grading system was useful.

(Allergy Asthma Proc 32:288–294, 2011; doi: 10.2500/aap.2011.32.3446)

Subcutaneous allergen immunotherapy (SCIT) is an efficacious approach to treat allergic rhinitis, allergic asthma, and Hymenoptera hypersensitivity.^{1–3} It may also be effective in preventing the onset of allergic diseases.^{4,5} With nearly 100 years of published data, beginning with the pioneering work by Noon⁶ and Freeman,⁷ SCIT is a relatively safe therapeutic option to treat these diseases. However, there is a risk for systemic reactions (SRs) associated with SCIT, which may range from mild to severe, including death. The authors of the 2007 update to the American Academy of Allergy, Asthma, and Immunology–American College of Allergy, Asthma, and Immunology practice parameters for immunotherapy recommend immediate intramuscular (i.m.) epinephrine as the treatment of choice for anaphylaxis.³ Additionally, the authors acknowledge that antihistamines and systemic corticosteroids may be used as secondary medications but are not a substi-

tute for epinephrine.³ For milder SRs (worsened rhinitis, urticaria, or mild wheezing or chest tightness) the use of epinephrine is more controversial. Because of the risk of a SR, the authors recommend patients remain in the physician's office for 30 minutes after an injection.³ The purpose of this study is to determine the response to immediate i.m. epinephrine for any reported sign or symptom of a SR after outpatient SCIT over a 1-year period.

METHODS

This retrospective study was designed to evaluate SRs to (build-up dosing and/or maintenance dose) the highest tolerated dose of SCIT with any combination of ~20 allergens (pollens, dust mites, cockroaches, animal dander, molds, and Hymenoptera) over a 1-year period (March 1, 2008–February 28, 2009). The study was approved by the University of South Florida College of Medicine Institutional Review Board and was conducted in a single four-physician allergy/immunology group practice associated with the University of South Florida. Informed consent was not required because this was a retrospective chart review and did not affect clinical practice. There are three separate clinics in the Tampa Bay area where patients are seen. Male and female adult and pediatric patients receiving SCIT were included. Aeroallergen, Hymenoptera, and imported fire ant (*Solenopsis invicta*) extracts were provided by Greer

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Funding for this article originated at the University of South Florida

The authors have no conflicts to declare pertaining to this article

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Systemic Reactions to Allergen Immunotherapy

Name _____ MR# _____

Build up _____ or _____ Maintenance _____

Approximate minutes after shot _____

History of Asthma: Yes _____ No _____

Signs and Symptoms (circle):

Respiratory	Skin	Eye/Nasal	Vascular	Other
Shortness of breath	Hives	Runny nose	Hypotension	Difficulty swallowing
Wheezing	Angioedema	Red eyes	Chest discomfort	Abdominal pain, nausea, diarrhea
Cough	Generalized itch	Congestion	Dizziness	Diffuse sweating/diaphoresis
Stridor/hoarseness	Flushing	Sneezing	Headache	Lightheadedness
Chest tightness	Rash	Itchy eyes/nose/throat		
Other _____				

Adult/child _____ lot # & exp. date _____

BP _____	P _____	Time _____	Epinephrine _____	_____
BP _____	P _____	Time _____	Epinephrine _____	_____
BP _____	P _____	Time _____	Epinephrine _____	_____
BP _____	P _____	Time _____	Epinephrine _____	_____

Time: _____

_____ Prednisone 10 mg/20 mg

_____ Prelone 1 tsp / 2 tsp / other _____ tsp / Pediapred 1 tsp / 2 tsp / other _____ tsp

_____ Antihistamine: Claritin 5mg/ 10 mg other _____ Clarinex 5mg / other _____

_____ Zyrtec 2.5 mg/ 5mg/ 10 mg other _____

_____ Allegra 30mg / 60 mg/ 180 mg other _____

_____ Oral suspension: Claritin 1mg/ml dose _____ Zyrtec 5mg/ml dose _____

_____ Nebulizers: Accuneb 0.63/ml or 1.25/3ml neb # of treatments _____

_____ Xopenex 0.31 mg/3ml or 0.63 mg/3 ml or 1.25 mg/3ml # of treatments _____

_____ MDI: Albuterol / Maxair # of inhalations _____

_____ IV- What type _____

_____ O2 _____

_____ Other treatment: _____

Figure 1. Form for recording symptoms and treatment provided.

Laboratories (Lenoir, NC) and dog extracts were provided by Hollister-Stier (Spokane, WA) and ALK Abello (Round Rock, TX).

According to clinic policy, nurses monitor patients given SCIT for a period of 30 minutes after injection. The reactions of patients who report symptoms and the treatment provided were recorded at the time of the reaction on a standardized form (Fig. 1). For the purposes of this study, SCIT-associated anaphylaxis was defined as signs or symptoms involving the following systems: cutaneous (other than at injection site), upper respiratory, ocular (conjunctival), lower respiratory, gastrointestinal, reproductive (uterine cramps or vaginal itching), and cardiovascular. Nurses were instructed to administer 0.2 mL of i.m. epinephrine (1 mg/mL) immediately into the deltoid or anterior-lateral thigh for any signs or

symptoms of a SR. The 1st dose of epinephrine was usually given i.m. in the deltoid muscle; repeat doses were given i.m. in the anterior-lateral thigh. All patients received standard supportive care in the clinic's emergency treatment room, *i.e.*, they were placed in the recumbent position with elevated lower extremities and repeat vital signs and clinical status were monitored.

At the conclusion of the study period and after institutional review board approval, the charts of all patients with reported SRs were reviewed for pertinent historical information. Particular attention was focused on the dose and dilution of the injection given, the interval between injections, and the dose of the subsequent injections after the SR. SRs were graded using the universal grading system proposed by the World Allergy Organization (WAO)⁸ (Table 1).

Table 1 World Allergy Organization subcutaneous immunotherapy systemic reaction grading system

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
The time of onset of symptoms should be included with the systemic reaction grade				
Symptom(s)/sign(s) of one organ system present	Symptom(s)/sign(s) of more than one organ system present	Lower respiratory Asthma (e.g., $\geq 40\%$ PEF or FEV ₁ drop, NOT responding easily to an inhaled bronchodilator)	Lower or upper respiratory Respiratory failure with or without loss of consciousness	Death
Cutaneous				
Generalized pruritus, urticaria, flushing, generalized sensation of heat or warmth*	or			
	Lower respiratory	or	Cardiovascular	
	Asthma: cough, wheezing, shortness of breath (e.g., $\geq 40\%$ PEF or FEV ₁ drop, responding to an inhaled bronchodilator)	Upper respiratory Laryngeal, uvula, or tongue edema with or without stridor	Hypotension with or without loss of consciousness and/or	
Angioedema (not laryngeal, tongue, or uvular)	or		Respiratory collapse/hypotension and/or	
Upper Respiratory			Loss of consciousness	
Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)	Gastrointestinal			
or	Abdominal cramps, vomiting, or diarrhea			
Throat clearing (itchy throat)	or			
or	Other			
Cough perceived to originate in the upper airway	Uterine cramps			
or				
Conjunctival				
Erythema, pruritus, or tearing				
Other				
Nausea, metallic taste, or headache				

These symptoms may progress rapidly to anaphylaxis.

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

Table 2 Demographics of subjects with systemic reactions classified by WAO grade

Age/Sex	Date	Diagnosis	Minutes after Injection	Symptoms (most prominent/severe)	Total Epinephrine Given (mg)	Grade
20 yr/o F	4/7/08	Allergic rhinitis	<1	Hives, SOB, and hypotension	1	4
38 yr/o F	4/25/08	Allergic rhinitis	10	SOB, chest tightness, and hypotension	0.9	4
37 yr/o M	10/17/08	Allergic rhinitis	45	Cough, hives, and hypotension	0.2	4
38 yr/o M	10/24/08	Allergic rhinitis	60	Angioedema and chest discomfort	0.2	3
26 yr/o F	2/2/09	Allergic rhinitis	15	Hoarseness/stridor and chest tightness	0.2	3
44 yr/o M	3/14/08	Allergic rhinitis	60	Hives, SOB, and wheezing	0.2	2
54 yr/o F	3/18/08	Allergic rhinitis	45	Hives and SOB	0.3	2
56 yr/o F	4/1/08	Allergic rhinitis	10	Cough and throat drainage	0.2	2
48 yr/o F	4/4/08	Allergic rhinitis	15	Cough and chest tightness	0.2	2
27 yr/o F	4/7/08	Allergic rhinitis	10	Chest discomfort and diff. swallowing	0.4	2
49 yr/o F	6/3/08	Allergic rhinitis	15	SOB and congestion	0.2	2
33 yr/o M	4/21/08	Allergic rhinitis	N/R	Cough, upper airway pruritus	0.2	2
6 yr/o F	5/2/08	Allergic rhinitis	40	Cough, generalized itching, and upper airway pruritus	0	2
57 yr/o F	6/30/08	Allergic rhinitis	10	Heart racing and diaphoresis	0.1	2
63 yr/o F	8/11/08	Allergic rhinitis	20	Chest tightness and abdominal pain	0.2	2
10 yr/o M	9/19/08	Allergic rhinitis	10	SOB, wheezing, and cough	0.4	2
36 yr/o F	10/29/08	Allergic rhinitis	1	SOB, wheezing, cough, chest tightness, and abdominal pain	0.4	2
36 yr/o F	1/13/09	Allergic rhinitis	40	Wheezing, cough, and upper airway pruritus	0	2
39 yr/o F	4/7/08	Allergic rhinitis	30	Upper airway pruritus and headache	0.3	1
37 yr/o F	6/30/08	Allergic rhinitis	8	Generalized itching	0.2	1
37 yr/o F	7/16/08	Allergic rhinitis	10	Generalized itching	0.3	1
33 yr/o M	7/28/08	Allergic rhinitis	N/R	Vasovagal syncope and "seizure"	0.2	1
51 yr/o M	8/11/08	Allergic rhinitis	30	"Heavy head"	0.2	1
57 yr/o M	8/25/08	Venom hypersensitivity	5	Generalized itching and upper airway pruritus	0.2	1
74 yr/o M	9/4/08	Allergic rhinitis	N/R	Sneezing and upper airway pruritus	0.2	1
50 yr/o F	9/17/08	Allergic rhinitis	120	Hives	0	1
25 yr/o F	11/5/08	Allergic rhinitis	10	Generalized itching sneezing	0.2	1
20 yr/o F	11/7/08	Allergic rhinitis	30	Upper airway pruritus	0.2	1
32 yr/o F	10/27/08	Allergic rhinitis	20	Generalized itching	0.2	1
75 yr/o F	11/11/08	Allergic rhinitis	20	Rhinorrhea and upper airway pruritus	0.2	1
38 yr/o F	12/31/08	Allergic rhinitis	5	Hives and rhinorrhea	0.5	1
33 yr/o F	2/17/09	Allergic rhinitis	2	Generalized itching and large local reaction	0.3	1

SOB = shortness of breath; N/R = not recorded.

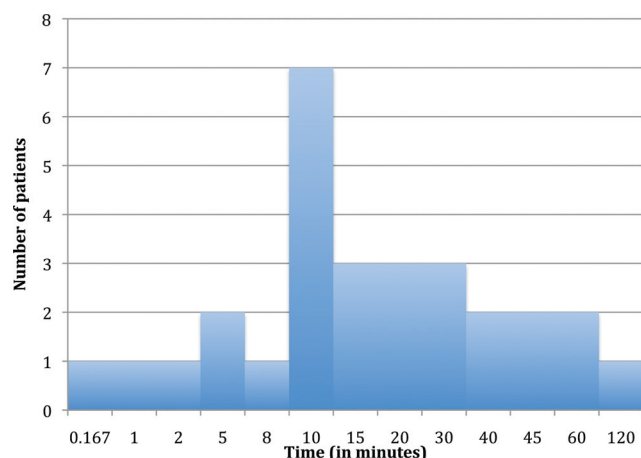


Figure 2. Time of onset of systemic reactions.

RESULTS

Seven-hundred seventy-three subjects, representing 14,707 patient visits, received ~28,000 injections over the 1-year study period. During the same period, 31 patients (4%) experienced 32 SRs (22 [71%] female and 9 [29%] male patients; average age, 40 years [range, 6–75 years]). This is a SR incidence rate of 1/460 patient visits (0.2%) and 1/875 injections (0.11%). Thirty-one reactions (97%) were in patients with a diagnosis of allergic rhinitis, receiving aeroallergen SCIT and one SR (3%) in a patient with Hymenoptera allergy receiving venom immunotherapy. Nineteen patients (61%) had a history of asthma; seven patients (22.6%) had a history of a previous SR to SCIT. Eighteen patients (56%) were receiving build-up and the remaining 14 (44%) were receiving maintenance immunotherapy.

Using the WAO grading system, 14 SRs were classified as grade 1 reactions (44%), 13 were grade 2 (41%), 2 were grade 3 (6%), and 3 were grade 4 (9%) reactions (Table 2). SRs were reported on average 24 minutes after injection (range, <1–120 minutes; Fig. 2). Thirteen reactions (41%) were reported with onset 0–10 minutes, six reactions (19%) were reported with onset 11–20 minutes, three reactions (9%) were reported with onset 21–30 minutes, and seven reactions (22%) were reported after 30 minutes had passed (these patients returned to clinic after symptoms started). The time to onset of symptoms was not recorded in three patients. Although one reaction started 120 minutes after the injection(s), no biphasic or late-phase reactions were reported. There were no fatalities.

Symptoms and signs reported include, in decreasing order, generalized pruritus, 34.4%; upper airway pruritus, 28.1%; cough, 25.0%; shortness of breath, 21.9%; chest tightness, 18.8%; generalized urticaria, 18.8%; sneezing, 15.6%; generalized flushing, 12.5%; wheezing, 12.5%; and “other rash,” 12.5% (Table 3). Twenty-five patients (78.1%) were receiving two injections at

Table 3 Reported symptoms and signs during SR and SCIT

Symptom/Sign	No. of Reactions*	Percent of Reactions
Generalized itching	11	34.4
Upper airway pruritus	9	28.1
Cough	8	25.0
Shortness of breath	7	21.9
Chest tightness	6	18.8
Urticaria	6	18.8
Sneezing	5	15.6
Flushing	4	12.5
Wheezing	4	12.5
Rash	4	12.5
Difficulty swallowing	3	9.4
Chest discomfort	3	9.4
Rhinorrhea	3	9.4
Lightheadedness	3	9.4
Hypotension	3	9.4
Congestion	2	6.3
Abdominal pain/nausea	2	6.3
Red eyes	1	3.1
Dizziness	1	3.1
Headache	1	3.1
Diaphoresis	1	3.1
Stridor/hoarseness	1	3.1
Other (throat drainage, heart racing, seizure, heavy head, dry mouth, lump in throat, scratchy throat, and/or voice change)	9	28.1

*Some patients experienced more than one symptom/sign simultaneously.

the time of SR. The most common dilution given was the red vial, 1:1 v/v (57.9% of vials).

Twenty-nine of 32 SRs (90.6%) were treated immediately with i.m. epinephrine; one of these patients received a dose of 0.1 mL of epinephrine, one 0.4 mL, and all others received 0.2 mL (Table 4). Twenty-seven (84%) of 32 SRs were treated with oral or i.m. glucocorticosteroid, 30 (94%) were treated with oral or i.m. H₁-antihistamine, and 9 (28%) were treated with a nebulized β-agonist. Nine reactions (28%) were treated with more than 1 dose of epinephrine because of persistent symptoms.

Three of 32 (9.4%) SRs were not treated with epinephrine. A 36-year-old woman experienced cough, wheezing, and upper airway pruritus after two SCIT injections and was treated with oral loratadine, 10 mg, and nebulized levalbuterol, 1.25 mg, after refusing epinephrine. A 6-year-old female patient experienced

Table 4 Medications used to treat systemic reactions

Treatment	No. of Reactions	Percent of Reactions
Oral or i.m. H ₁ -antihistamine	30	93.8
Epinephrine	29	90.6
Oral or i.m. glucocorticosteroid	27	84.4
Nebulized or inhaled β-agonist	9	28.1

i.m. = intramuscular.

cough and generalized pruritus 40 minutes after her two SCIT injections and was treated with oral loratadine, 10 mg. The reason this patient did not receive epinephrine was not recorded. A 50-year-old woman experienced urticaria and generalized pruritus 120 minutes after two injections of SCIT and was treated with oral prednisone, 20 mg, and oral diphenhydramine, 50 mg. Epinephrine was not given because of the delayed onset of symptoms. The symptoms and signs of all patients fully reversed with treatment.

Three SRs were classified as grade 4, as defined in the WAO grading system for subcutaneous immunotherapy-induced anaphylaxis, and two were treated with multiple doses of epinephrine. Notably, all three patients presented with cutaneous symptoms. The first of these three patients is a 38-year-old woman who developed generalized pruritus, shortness of breath, and hypotension (90/60 mmHg) within 10 minutes of receiving two injections of 0.25 mL from 1:1 v/v vials. Her symptoms and signs responded to 4 doses of i.m. epinephrine, given in the following manner 5–10 minutes apart: 0.2, 0.2, 0.2, and 0.3 mL. She also received oral prednisone, 20 mg; oral loratadine, 10 mg; and 2 doses of nebulized levalbuterol, 1.25 mg. She was transferred to a local emergency department for observation and subsequently released. SCIT was discontinued by her physician.

A second patient, a 20-year-old woman, experienced shortness of breath, conjunctivitis, and diffuse urticaria within 10 seconds (as documented by the nurse) after SCIT with two injections from 1:1 v/v vials, 0.15-mL build-up. She developed hypotension (90/40 mmHg) and was treated with 5 doses of i.m. epinephrine in the following manner over 30 minutes: 0.2, 0.3, 0.2, 0.2, and 0.1 mL. She also received 3 doses of oral prednisone, 20 mg; methylprednisolone, 40 mg i.m.; diphenhydramine, 25 mg i.m.; and i.v. fluids. All symptoms fully resolved in the clinic; her treating physician discontinued SCIT.

The third patient, a 37-year-old man, presented with cough, chest discomfort, and generalized urticaria 45

minutes after receiving two 0.2-mL injections from 1:1 v/v during build-up. He left the clinic without symptoms after waiting 30 minutes but returned after symptoms began. The patient subsequently developed hypotension (90/60 mmHg). He was treated with i.m. epinephrine, 0.2 mL; oral prednisone, 20 mg; and oral loratadine, 10 mg, with resolution of symptoms. SCIT was continued, with a decreased maintenance dose.

Three reactions were characterized by symptoms/signs not necessarily typical of an IgE-mediated allergic reaction. The first patient is a 33-year-old man who experienced syncope, interpreted as a vasovagal reaction, 30 minutes after two 0.5-mL injections from 1:1 v/v vials. He was treated only with epinephrine, 0.2 mL i.m. The second patient, a 57-year-old woman, developed heart racing, light-headedness, and sweaty palms 10 minutes after receiving 0.2 mL from 1:10 v/v and 0.15 mL from 1:1 v/v vials. She was on a modified rush protocol and had received her third set of injections within 1 week. She was treated with i.m. epinephrine, 0.1 mL. The third patient, a 51-year-old man, experienced a “heavy head” and dry mouth 30 minutes after receiving two 0.03 mL injections from 1:100 v/v vials. He was treated with i.m. epinephrine, 0.2 mL; oral prednisone, 20 mg; and oral loratadine, 10 mg. After treatment, the symptoms and signs of all three patients resolved and all three patients continued SCIT.

DISCUSSION

Previous studies report varying occurrence of SRs after SCIT. A 1992 review of 38 studies using conventional SCIT by Stewart and Lockey⁹ reported a mean occurrence of SRs of 12.9% of patients receiving SCIT (range, 0.8–46.7%) and in a mean of 0.5% of injections (range, 0.05–3.2%). When rush or semirush protocols were used, the mean occurrence was 2.36% of injections (range, 0–6.4%).⁹

Other large prospective and retrospective studies report varying occurrences of SRs, from 2.12¹⁰ to 18%¹¹ of patients, 0.043¹² to 1.3%¹³ of patient visits, and 0.025¹² to 0.49%¹¹ of injections. This variation in the reported incidence of SRs may be caused by several factors: underreporting by patients, variation in prescribing patterns and preparation of vials for SCIT, and/or disagreement among physicians about the definition of anaphylaxis.

Biphasic SRs after SCIT occur in 10¹³ to 23%¹⁴ of all SRs according to published reports, with most of the reactions described as mild. Potential risk factors for biphasic reactions include concomitant asthma, low baseline peak expiratory flow,¹³ female gender, and the requirement for ≥2 doses of epinephrine¹⁴ to treat the initial SR. Patients in our study were not contacted after an SR to make inquiry concerning delayed or biphasic SRs; however, patients were asked to call the clinic to report such reactions.

To the authors' knowledge, this is the first study to incorporate the WAO subcutaneous immunotherapy SR grading system to assign a grade to each SR. Because the grading system was applied retrospectively, neither the order of onset/presentation of symptoms/signs nor the time to administration of epinephrine was recorded, preventing the assignment of a final grade (e.g., grade 2a; rhinitis, 10 minutes) for each reaction. However, the grading system was useful for documenting the severity of the reaction. The majority of reactions were mild (grades 1 or 2), but there were three potentially life-threatening (grade 4) reactions. Nearly all reactions were treated with epinephrine, with timely resolution.

This study has several limitations, most significantly its retrospective design. Prospective studies among SCIT patients are difficult to perform because all patients receiving SCIT would need to provide informed consent, even though the potential group of systemic reactors is small. Another limitation is the variation in treatment of systemic reactors, just as in clinical practice. Three patients presented with symptoms and/or signs typical of an IgE-mediated reaction but were not treated with epinephrine. Furthermore, three patients were treated with epinephrine despite having symptoms that were not necessarily typical of an IgE-mediated reaction. Also, there was some variation in the dosage of epinephrine given, ranging from 0.1 (0.1 mg) to 0.4 mL (0.4 mg) per dose. Incorporating the WAO grading system prospectively would standardize treatment protocols.

This study supports the recommendation of the "World Allergy Organization Ad Hoc Committee on Epinephrine and Anaphylaxis" that any symptoms of anaphylaxis associated with SCIT be treated immediately with i.m. epinephrine.¹⁵ As such, even if the first sign or symptom does not meet criteria for anaphylaxis (e.g., headache), epinephrine should be considered early, because the next sign or symptom may be severe (e.g., hypotension). Epinephrine has been shown to be safe, whereas failure to properly recognize and treat anaphylaxis may have dire consequences.¹⁶ Furthermore, the dose of epinephrine given can be titrated to the SR according to the patient's symptoms; this study indicates a starting dose of 0.2 mL (0.2 mg) is effective in a majority of patients.

In summary, SRs occurred in 4% of patients receiving SCIT and in 0.11% of injections given over a 1-year period. Immediate use of i.m. epinephrine at the first sign of reaction was associated with prompt resolution of signs

and symptoms. The WAO subcutaneous immunotherapy systemic reaction grading system was an effective method of retrospectively classifying reaction severity.

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