

Improving the Safety of Immunotherapy

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We present a 42-year-old woman who experienced a systemic reaction (SR) after a subcutaneous immunotherapy (SCIT) injection. Her physician must make a decision, along with the patient, on how to proceed. We consider the medical evidence pertinent to specific risk factors for SRs to SCIT, including asthma control, concomitant medications and new medical diagnoses, the influence of pollen season, adjustments for large local reactions, initial testing results, type of buildup protocol, and administration and dosing errors. We next discuss the potential risk-mitigating actions that the patient and provider should consider and the available evidence that supports various approaches, including cessation of SCIT, decreasing allergen dose or altering the timing of injections, initiating or changing the medical pretreatment regimen, and changing to sublingual immunotherapy, and also the role for anaphylaxis preparedness. Finally, we highlight the key knowledge gaps identified in this review and provide management recommendations for this 42-year-old woman. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:131-5)

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A 42-year-old woman with a history of allergic rhinitis and asthma presented for a follow-up visit after having a systemic reaction (SR) to a subcutaneous allergen immunotherapy (SCIT) injection. She had received 3 oral corticosteroid courses over the past year for asthma exacerbations and used a rescue inhaler approximately 3 times per week for breakthrough symptoms of shortness of breath and wheezing. Three days earlier, she received 0.10, 0.15, and 0.25 mL, each separated by 30 minutes, of a

1:10 dilution vial (as part of a cluster buildup protocol). The vial contained 5 different pollen extracts at doses recommended by recent allergy practice parameters.¹ Five minutes after receiving the final injection on that day, she reported flushing, nasal congestion, nasal itching, and chest tightness with wheezing. She was treated immediately with 0.3 mg epinephrine intramuscular (lateral thigh), diphenhydramine 50 mg intramuscular, prednisone 40 mg orally, and 6 puffs of inhaled albuterol. Her symptoms improved over the course of 5 minutes. She was observed for 3 hours in the clinic before she was discharged home with careful instructions on how to recognize symptoms that would warrant immediate medical attention.

RISK ASSESSMENT FOR SRs TO IMMUNOTHERAPY INJECTIONS

Each patient considered for SCIT should have a baseline assessment for individual risk of SRs. Several contributing factors for life-threatening SRs to SCIT injections have been identified (Table I). However, based on prior surveys of fatal and near-fatal SCIT reactions, contributing factors for severe SRs cannot always be clearly identified.^{2,3} Before initiating treatment, the risk of SR during SCIT should be discussed with patients relative to the potential treatment benefit. The incidence of SRs for SCIT is 1 in 500 to 1 in 1000 injections (0.1%-0.2%), an incidence derived by using predominantly nonaccelerated buildup schedules.¹ The approximate risk of death after a SCIT injection is 1 in 2,500,000 injections,^{2,4,5} although analysis of recent data suggests that this risk may be decreasing.⁶ Identified risk factors that possibly contribute to fatal reactions after SCIT injections include poorly controlled asthma, previous systemic reactions, dosing errors, dose administered during peak pollen seasons, concomitant use of β -blockers, a high degree of skin test sensitivity, freshly prepared extracts, and administration of injections in medically unsupervised settings.^{2,4,5} Risk factors for near-fatal reactions were similar to those for fatal reactions, with the addition of premature clinic departure before the customary waiting period.⁵ Providers should conduct an individual risk assessment that considers these risk factors in each patient before initiating SCIT.

The following questions pertinent to risk should be considered in all patients after an injection-related SR (Table II): (1) was asthma uncontrolled or exacerbated at the time of the injection; (2) did the patient start any new medications (eg, β -blockers, angiotensin-converting-enzyme inhibitors) or receive any new medical diagnoses; (3) does the patient usually premedicate before SCIT injections, and did she remember to this time; (4) did the SR occur during a relevant peak pollen season, and was the dose adjusted for the pollen season; (5) did the patient have a history of large local reaction (LLR) or SR before the current reaction; (6) at what dose during the buildup or maintenance phase did the SR occur; (7) was the injection given from a freshly prepared vial; if yes, was a dose adjustment made; (8) did the SR

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Abbreviations used

AIT- Allergen immunotherapy
FEV₁- Forced expiratory volume in 1 second
IT- Immunotherapy
LLR- Large local reaction
SCIT- Subcutaneous allergen immunotherapy
SLIT- Sublingual immunotherapy
SR- Systemic reaction

begin after the customary waiting period; and (9) was the right dose administered to the right patient or was there a dosing error?

MEDICAL EVIDENCE PERTINENT TO SPECIFIC RISK FACTORS THAT CONTRIBUTE TO SRs

Asthma control

An assessment of asthma control is recommended (by using recent guideline definitions of asthma control) in all patients with asthma before administration of each SCIT injection.¹ Uncontrolled asthma has clearly been associated with near-fatal and fatal SRs.²⁻⁵ A prospective study conducted in individuals who received SCIT with dust mites when using a rush protocol suggests that an FEV₁ < 80% predicted significantly increased risk of SRs.⁷ Individuals with FEV₁ measures of <70% predicted may require additional consideration for risk modification (or may not have favorable risk:benefit ratios for AIT [allergen immunotherapy]).¹ Patients with unstable asthma generally should not be considered for SCIT, barring exceptional circumstances. A recent North American study finding of high rates of asthma screening before SCIT injections suggests that near universal asthma screening by allergists may be an important factor in the declining rate of fatal reactions.⁶ Asthma can be assessed by a symptom questionnaire and/or objective measures of airway obstruction (peak flow or spirometry). Analysis of the most recent survey data suggests that 33% of practices screen patients with objective measures of airway obstruction and that 86% screened for asthma symptoms.⁶ There are no studies that compared outcomes of preinjection screening for symptoms alone versus assessing symptoms and lung function. We recommend that, ideally, both methods be used and that each clinic that administers SCIT has a protocol that delineates peak flow and spirometry results, and asthma symptoms that require review by the physician before administering an injection.

The role of concomitant medications and new medical diagnoses

Concomitant use of β -blockers can make anaphylaxis after SCIT injections more difficult to treat, although this notion is primarily based on research performed in anaphylactoid reactions to radiocontrast media.⁸ A case report highlights the potential risk of using SCIT in patients with asthma who are taking nonselective β -blockers.⁹ Immunotherapy (IT) is relatively contraindicated and not recommended for patients with asthma who are receiving β -blockers. Prospective studies of patients who receive SCIT suggest no increased risk of SR frequency.¹⁰ In patients who require Hymenoptera IT for prevention of anaphylaxis from Hymenoptera stings and in whom discontinuation of β -blockers is medically contraindicated, the benefit of IT for prevention of anaphylaxis may outweigh the low theoretical risk of ongoing use of a β -blocker. There is medical

TABLE 1. Factors that should be considered in the initial risk assessment for systemic reactions to SCIT

Risk factors	Reference nos.
Poorly controlled asthma	2-7
Previous systemic reactions	2, 4, 5
Concomitant β -blocker use	8, 10
Administration in an unsupervised setting	2, 4, 5
Comorbid illness (eg, cardiac and/or pulmonary)	2-7, 12
Pregnancy	1
High degree of allergen sensitivity	4, 5, 19
Baseline serum tryptase (for venom IT)	9

evidence that suggests that the risk of severe SRs associated with Hymenoptera venom IT is increased in patients who receive ACE inhibitors,¹¹ but ACE inhibitor treatment has no effect on the frequency of SRs.¹² Individuals who have comorbid diagnoses of cardiac disease, neoplasm, or autoimmune disease have unknown risks associated with SCIT. The SCIT experience of individuals with these conditions have been reported, and the overall risks of major and minor problems based on survey data are low.¹³ In general, SCIT should be avoided in patients with comorbid conditions that could reduce the likelihood of surviving a severe anaphylactic reaction.

The influence of pollen season on SRs

There are no randomized studies that compare the effect of adjusting SCIT doses downward during pollen seasons versus continuing regular doses. However, analysis of retrospective data suggests that dose adjustment during pollen season may modify the risk of SRs. Reid et al⁵ reported that 5 of the 17 fatalities associated with SCIT SRs occurred during the allergy season. Bernstein et al² reported an analysis of 17 fatalities associated with SCIT, 3 of which occurred at the height of the pollen season. Amin et al³ reported that 46% of survey responders reported that a near-fatal SR occurred at the height of allergy season. Epstein et al⁶ found that practices that always reduced AIT doses during pollen seasons had 21% fewer grades 2 and 3 SRs. However, despite these associations that have been consistently found in survey studies, 2 large prospective studies found no association between SRs and pollen season.^{14,15} There are 3 potential ways to use this information in an SCIT practice: (1) do not adjust because no prospective evidence demonstrates differences in SR outcomes, (2) adjust in those individuals who have had an SR during the pollen season, or (3) adjust for all patients during pollen seasons. We recommend that practices consider a customized approach, such as routinely adjusting doses during the individual patient's peak pollen season, although we recognize that the medical evidence that supports this approach is conflicting. If a patient has an SR during peak pollen season, we recommend adjusting doses during future peak pollen seasons during the remainder of the SCIT course. If an SR occurs despite dose adjustment, then options include stopping the SCIT or considering other risk mitigation options.

LLRs

LLRs are defined as welts at the site of injection that are larger than the size of a human palm (>25 mm by 25 mm in welt diameter) and the absence of systemic symptoms. There is not clear guidance on whether adjusting for LLRs influences the risk

TABLE II. Strategies to modify the risk of systemic reactions to AIT

Modification strategies	Reference nos.	Modification strategies	Reference nos.
Screen for poor asthma control at each visit	2-7	Premedication	24-27
Adjust buildup protocol	1, 6, 20, 21	Eliminate wrong doses	3, 2, 23
Adjust dose during pollen season	2, 5, 6	Discontinue in patients on β -blockers	8
Adjust for large local reactions	15-18	Epinephrine autoinjector available after waiting period	1, 33, 34
Adjust with freshly prepared vials	1	Anaphylaxis preparedness	

of future SRs. Two retrospective studies found that adjustment of an AIT dose based on LLRs did not influence SR rates.^{16,17} Another retrospective study found a higher rate of LLRs in those who ultimately experienced an SR.¹⁸ Calabria et al¹⁹ studied individuals who have had both LLR and SR, and compared with a control group of subjects who had an SR but no LLR. They found that the rate of SR was 1.3% for those with a previous LLR compared with 0.4% for those without an LLR. They further were able to identify a subgroup of individuals who had frequent LLRs and an increased SR risk. These studies, taken together, do not provide adequate evidence to recommend routine SCIT dose adjustments for LLRs.

Initial skin testing results and risk for SRs

Lockey et al⁴ reported that 11 of the 24 fatalities identified had high degrees of sensitivity and that 12 of 17 fatalities reported by Reid et al⁵ had high degrees of sensitivity based on baseline skin test results. In a retrospective review of 16,375 SCIT injections, 20 patients experienced 46 SRs.²⁰ Compared with matched controls, patients who had 33% or more 3 to 4+ pre-IT aeroallergen skin tests had a 6-fold higher likelihood of an SR, with the risk increasing by 17% for each additional 4+ skin test.²⁰ Whether starting patients with high and multiple skin test sensitivities at lower doses, avoiding accelerated dosing protocols, or using routine premedication is effective at reducing frequency and/or severity of SRs is unknown because prospective studies have not addressed these questions. For Hymenoptera IT, a baseline serum tryptase may predict subsequent SRs and may also lead to a diagnosis of systemic mastocytosis in a small percentage of patients.¹¹ Prospective studies have not been conducted to determine if pretreatment screening with serum tryptase is a significant predictor for SRs.

Type of buildup protocol (standard vs accelerated)

SRs can occur during buildup or maintenance phases of SCIT. Different means of proceeding through the buildup phase include standard slow versus accelerated cluster and rush protocols. Analysis of the literature suggests that rush IT involves a higher risk of SRs than standard slower buildup protocols and, therefore, should be approached with caution and that aggressive premedication may be considered.¹ The risks of SR with cluster IT are less clear. Results of 1 study suggest a similar risk as standard buildup protocols, especially if premedication is used.²¹ A retrospective review of a multicenter allergy practice in the United States identified 441 patients who received multiallergen SCIT by using a cluster buildup protocol, noting that 10.9% reported an SR.²¹ Notably, only 10.6% of these were grade 3 SR, and 2.1% were grade 4 (no grade 5 was reported). As defined in the article by the World Allergy Organization, grade 3 SRs involved lower or upper respiratory symptoms, grade 4 involved respiratory failure without loss of consciousness or hypotension,

and grade 5 death.²² Epstein et al¹⁶ also found a significantly higher risk of grade 1 and 2 SRs in practices when using cluster or rush buildup protocols than those practices that only used standardized protocols; this did not seem to be modified by the use of premedication or in practices with lower target doses (D. Bernstein, personal communication). Therefore, the risk of SR is likely higher with cluster and rush buildup protocols.

Administration and dosing errors

SRs can occur if patients receive a higher dose than recommended or if they receive another patient's SCIT dose. Amin et al³ reported that 25% of near-fatal reactions to SCIT were associated with dosing errors. Aronson and Gandhi²³ surveyed allergists and reported, in 2004, that 74% had reported at least 1 incorrect-dose injection given to their patients over a 5-year period. In a systems-based analysis of 1 center's SCIT practice, the SCIT administration error rate was 0.1%-0.2%.²⁴ The 2 most common circumstances in which errors were committed were when patients were treated with an atypical dosing protocol and with extract vial changes. When dosing errors are recognized in an SCIT practice, a systems analysis is recommended that maps processes coupled with error analysis.

RISK MANAGEMENT: POTENTIAL ACTIONS OR INTERVENTIONS AFTER AN SR TO IT

Stopping IT

Depending on the severity of the SR and the risk tolerance of the patient and the provider, discontinuation of SCIT should be considered after an SR. The risks of a second SR after having at least 1 previous SR are not well described, although a history of a previous SR was found to be a contributing factor to fatal or near-fatal reactions.^{1,2} Patients who were at high risk on the baseline assessment and who already had had several risk modification strategies in place may have a risk that outweighs the potential benefit of SCIT.

Decrease allergen dose

There is little evidence to provide guidance for dose modification. A common practice is to decrease the dose and rebuild after an SR. The dose can be reduced 1 vial (10-fold dilution) or to a previously tolerated dose. Another option is to decrease the dose and leave it at the decreased dose with plans for rebuilding at a later time (perhaps after the pollen season is over). There are no trials that compared this approach with continuing the current dose (or resuming a buildup schedule).

Initiate or change a medical pretreatment regimen

Pretreatment with H1 antagonists likely decreases the risk of SRs when used in accelerated AIT schedules;²⁵ only 1 study has demonstrated benefit by using standard AIT schedules.²⁶ However, it is not clear if premedication prevents the most severe SRs.

Patients may be taking H1 antagonists before AIT injections but then forget; therefore, it is important to inquire about adherence to the premedication regimen. Omalizumab has been shown to reduce SRs in accelerated schedules²⁷ and in standard schedules,²⁸ although it is only currently labeled in the United States for use in asthma. We were unable to identify studies that adequately addressed the potential role of higher doses of H1 antagonists, H2 antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, and nonsteroid anti-inflammatory drugs for preventing future SRs. Use of these medications may still be considered, although only after a discussion of the uncertainty of effect.

Change to sublingual IT

Recently published sublingual IT (SLIT) trials have confirmed that SRs are extremely rare.²⁹⁻³² A case report of an individual who had been treated with SCIT and had an SR, and who then tried SLIT and had an SR suggests that caution may be needed when transitioning high-risk individuals to SLIT.³³ More data that report risks of SLIT in patients who have had an SR to subcutaneous AIT are needed because SLIT trials have generally excluded such patients. Therefore, although analysis of SLIT trial data suggests low SR rates, the SR rate for individuals who have experienced an SR to SCIT is not established. At this time, SLIT formulations are not approved by the US Food and Drug Administration for use in the United States.

The role of anaphylaxis preparedness and prompt administration of epinephrine

In a recent report, Phillips et al³⁴ described treatment of 32 individuals with SRs and found that all who received epinephrine promptly had a successful outcome. Administering SCIT while in a location where anaphylaxis can be recognized and promptly addressed is a key safety feature of an excellent SCIT program. Practices that administer SCIT should periodically evaluate their treatment responses to SRs and make adjustments to ensure they are in line with best practices put forward by practice parameters.¹

Another aspect of anaphylaxis preparedness is direct observation of individuals after SCIT injections.¹ In the most recent survey in North America that estimated the frequency of delayed SRs to SCIT (SRs that occur more than 30 minutes after injection), 289 (14%) had delayed-onset SRs compared with 1816 early-onset SRs (86%).³⁵ We recommend that patients wait 30 minutes (or longer) after SCIT injections and that consideration be given for prescribing an epinephrine auto-injector for high risk if not all patients on SCIT.

FUTURE RESEARCH NEEDS

A number of key questions that surround the safety of SCIT remain unanswered. Perhaps the largest gap in our knowledge in SCIT safety is which strategies to use when we identify a patient who is at higher risk of SRs or who has already had an SR. Although we know the clinically effective dose ranges of standardized allergens for SCIT, there is an unmet need to define the "therapeutic window" for dust mite, animal dander, and pollen allergens; that is, identifying those doses that provide both optimal safety and efficacy. We presented data to support various approaches, including cessation of SCIT (or never starting it), decreasing allergen dose or altering the timing of injections, initiating or changing the medical pretreatment regimen, or

changing to SLIT, as well as the role for anaphylaxis preparedness. There is a need to perform prospective studies to compare the effectiveness of these risk-mitigation strategies.

CASE RESOLUTION

There were several issues to consider with the 42-year-old woman who experienced an SR after SCIT. First, she was in the midst of building with a cluster protocol by using a multiallergen pollen vial, which likely confers a higher risk of SRs. Second, she had a history of asthma, which, if poorly controlled, could have contributed to an SR that was primarily a respiratory reaction. Review of her records revealed that she had been asked by the team about worsening asthma (no) and had performed a peak flow (average of 3) of 480 L/min (personal best, 500 L/min). Additional probing revealed that she had had an upper respiratory infection 1 week earlier and was having some persistent cough, which resulted in increased rescue inhaler use. Third, she was receiving pollen SCIT during the peak pollen season. An additional review included confirmation that she had received the right dose from her vial, that she had not been routinely premedicating on injection days, and that she had no new medications or diagnosed diseases. Taken together, a cluster buildup protocol during the peak pollen season and recently increased asthma symptoms were the most likely factors that contributed to the SR. However, SRs can occur in the absence of any risk factors, and, therefore, the attribution of risk factors is somewhat uncertain. The recommendations for this patient were (1) decrease dose by 1 vial (back to 0.2 mL of 1:100 vial), (2) rebuild with standard protocol beginning after the pollen season, (3) premedicate with H1 antagonist, and (4) institute more-intense asthma screening, which includes additional questions before each injection and monitoring of peak expiratory flow before each injection. The patient desired to continue with SCIT and agreed with the recommendations suggested by the provider.

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