

Paradigms and perspectives

Managing risk of anaphylaxis in patients receiving allergen immunotherapy: Assessing benefit versus risk

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Key words: Subcutaneous immunotherapy, anaphylaxis, injections, risk, systemic reactions

WHAT ARE THE RISKS OF SCIT AND SUBLINGUAL IMMUNOTHERAPY?

Allergy immunotherapy (AIT) is an effective treatment modality for allergic rhinitis, asthma and other allergic disorders.¹ Since its introduction in 1911, evidence supporting effectiveness of subcutaneous AIT or subcutaneous immunotherapy (SCIT) with aqueous allergen extracts has slowly emerged, mostly from small clinical trials, some of which were underpowered or lacked adequate controls. During the second half of the 20th century, placebo-controlled clinical trials began to define effective doses of specific therapeutic allergens and characterize their allergenic potency and major allergen content. The duration of treatment required for efficacy and sustained effectiveness after discontinuation of SCIT has been better defined for seasonal allergic rhinitis (ie, rhinitis due to grass pollen).

Therapeutic products for SCIT were developed before the advent of large phase 3 double-blind placebo-controlled multicenter trials, in which adverse effects could be systematically assessed. Soon after the introduction of SCIT into clinical practice, rare cases of severe anaphylaxis due to subcutaneous injections with aqueous pollen extracts were identified. Since 1945, cases of very rare fatal anaphylaxis have been documented via retrospective published surveys conducted among large samples of practicing allergists in North America.² Data from one such survey conducted between 1985 and 1989 enabled estimation of an incidence rate of approximately 1 fatal event occurring per every 2 million injections.³ A second survey of practicing allergists spanning 1990 to 2001 yielded an estimate of 1 fatal reaction (FR) per 2.5 million injection visits.^{2,3}

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Supported by grants from the American Academy of Allergy, Asthma & Immunology and the American College of Asthma, Allergy, and Immunology for conduct of the annual immunotherapy safety study and for statistical analysis as part of the National Surveillance Study on Immunotherapy (to T.G.E.).

Disclosure of potential conflicts of interest: D. I. Bernstein is a consultant, advisor, and speaker for ALK America. The remaining author declares that she has no relevant conflicts of interest.

Received for publication December 20, 2021; revised January 9, 2022; accepted for publication January 17, 2022.

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J Allergy Clin Immunol 2022;■■■:■■■-■■■.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2022.01.009>

These published cases also provided valuable insight into factors that treating allergists believed may have contributed to these unfortunate events (Table I).^{2,3} Above all, unstable, uncontrolled, labile, and severe asthma was the most consistently identified contributor in 62% of fatal reactors. Many of these patients had previously experienced emergency room visits and hospitalizations for acute asthma. Other commonly cited possible contributing factors included prior systemic reactions (SRs) to previous injections (reported in 53% of events), administration of the injection during peak allergy seasons (reported in 47% of events), dosing errors (reported in 35% of events), and suboptimal treatment of anaphylaxis (eg, delay in administration of epinephrine [reported in 43% of events]). Suboptimal, medically unsupervised settings (eg, injections given at home) or insufficient postinjection observation (in 21% of events) were cited as possible contributing factors. In 17% of events, no obvious contributing factor could be identified.

To better track severe SRs to SCIT injections and to gain insight into clinical procedures surrounding SCIT administration, annual surveys have been administered to North American allergists since 2008 as part of a project cosponsored by the American College of Asthma, Allergy, and Immunology and the American Academy of Allergy, Asthma & Immunology.⁴ Data from these surveys have defined risk for SCIT with multiple aqueous allergen extract mixtures as practiced in North America and cannot necessarily be extrapolated to European practices utilizing fewer allergens or modified allergens. During the first 12 years of the project, 10 new FRs to SCIT were confirmed, yielding an estimated incidence of 1 FR per 7.2 million injection visits. Asthma remained a consistently cited patient characteristic in recently reported FRs. Late recognition of anaphylaxis was implicated in 1 FR, and early departure by another patient from the injection facility prevented prompt treatment of fatal anaphylaxis.⁴ The estimated overall incidence of SRs of any severity was 1 in every 1000 injection visits (0.1 %) and 0.8% of patients receiving injections. Nearly all injection-related SRs were mild, either grade 1 or grade 2.⁴ The annual survey found that approximately 15% of SRs began more than 30 minutes after administration; most were mild SRs.⁵ The North American survey yielded an estimated incidence of near-fatal anaphylaxis (ie, defined as hypotension and/or respiratory insufficiency comparable to a grade 4 SR based on the World Allergy Organization grading system) of 1 event in every 160,000 injection visits (~0.01% of treated patients).⁴

Since 2008, annual surveys of allergists have largely reinforced what was already known about risk factors for SCIT anaphylaxis. In all, 50% percent of all severe grade 3 and grade 4 SRs were reported in patients satisfying the American Thoracic Society case definition for severe asthma.⁴ One survey of allergists showed that 34% of patients with severe SCIT-induced anaphylaxis had already experienced a prior SR to

TABLE I. Identified risk factors and prevalence in 34 cases of fatal anaphylaxis with SCIT injections reported between 1985 and 2001

Risk factor	Prevalence in 1985-2001 (n = 34)
Uncontrolled asthma	62%
Prior SR	53%
Peak pollen season	47%
Suboptimal treatment of anaphylaxis	43%
Dosing error	35%
<30 minutes of postinjection observation	12%
Injection given in a suboptimal setting (eg, home)	9%
Delayed reaction (>30 minutes of observation)	9%
No contributing factor identified	17%
β -Blocker/angiotensin-converting enzyme inhibitor	2%/2%

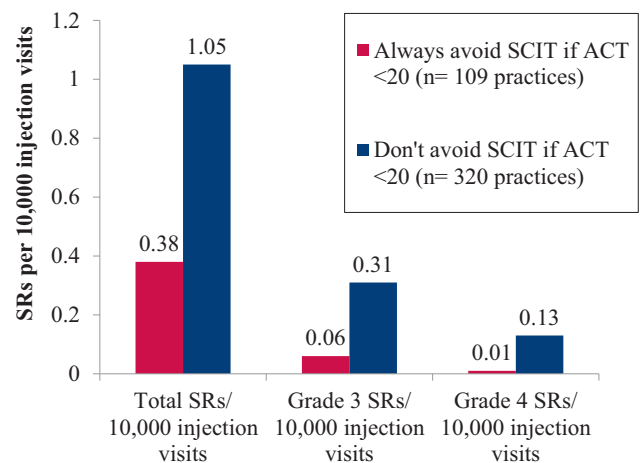
Data from Bernstein et al.² and Reid et al.³**TABLE II.** Key practice parameter recommendations for optimizing the safety of patients receiving subcutaneous allergy injections

1. Allergen immunotherapy in patients with asthma should not be initiated unless the patient's asthma is stable with pharmacotherapy (summary statement 16)
2. Although there is a low risk of severe SRs with appropriately administered AIT, life-threatening reactions and FRs do occur (summary statement 31)
3. Poorly controlled asthma has been identified as a risk factor for a severe immunotherapy-induced reaction. Before administration of the allergy injection, the patient should be evaluated for the presence of asthma symptoms. One might also consider an objective measure of airway function (eg, peak expiratory flow) for the patient with asthma before allergy injections (summary statement 32).
4. Because most serious SRs due to allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office/medical clinic for at least 30 minutes after the immunotherapy injection (summary statement 33)
5. Allergen immunotherapy should be administered in a setting in which procedures that can reduce the risk of anaphylaxis are in place and in which prompt recognition and treatment of anaphylaxis is ensured (summary statement 45)
6. Risk factors for fatal immunotherapy injections include delayed administration of epinephrine (summary statement 46)

Adapted from Cox et al.¹

SCIT. SRs were more common in allergy practices utilizing accelerated buildup schedules (ie, cluster or rush up dosing protocols) to initiate SCIT, although these were usually mild grade 1 or grade 2 SRs.⁶

Sublingual immunotherapy (SLIT) is an AIT treatment option that has gained regulatory approval worldwide on the basis of large well-powered double-blind placebo-controlled phase 3 clinical trials demonstrating both safety and efficacy for seasonal or perennial allergic rhinitis. Although anecdotal severe cases of anaphylaxis have been reported both with approved products and with off-label SLIT drops, none has been fatal. In separate clinical trials of SLIT house dust mite tablets designed to evaluate the tablets' efficacy in perennial allergic rhinitis and asthma, subjects with asthma reported frequencies of treatment-related adverse events equivalent to those reported by subjects without asthma, with no confirmed treatment-related asthma exacerbations.⁷

**FIG 1.** Practices that never start SCIT in patients with uncontrolled asthma (Asthma Control Test score <20) had a lower likelihood of grade 3 (odds ratio = 0.7 [95% CI = 0.5-1.0]) and grade 4 SRs (odds ratio = 0.3 [95% CI = 0.1-0.8]) or 70% fewer grade 4 SRs.⁹

MITIGATING RISKS WHILE OPTIMIZING BENEFITS OF AIT

A profile of the patient at higher risk for severe anaphylaxis associated with SCIT has emerged. Risk modification strategies to reduce severe SRs following SCIT injections are well delineated in the third update of AIT practice parameters (Table II) and in European guidelines.^{1,8} Many of these strategies are based on expert opinion, but recent evidence supports the effectiveness of some of these recommendations. Prescreening for loss of asthma control by assessing symptoms and/or lung function before administration of SCIT injections has been widely adopted by 86% of allergists. As shown in Fig 1, clinical practices choosing not to initiate SCIT in patients with uncontrolled asthma (ie, those with an Asthma Control Test score of <20) experience significantly fewer total and severe SRs.⁹ A survey of clinics in North America found that those who reduced or did not increase allergen doses during peak pollen seasons were less likely to report severe SCIT-related anaphylaxis.¹⁰ It is well established that nearly all severe reactions or FRs with SCIT begin within the first 30 minutes after injections were received. In a recent survey, those clinical practices that strictly monitor time after injections and require all patients to check out with nursing staff before exiting the injection site experienced significantly fewer grade 3 and grade 4 SRs than did those practices with more lax postinjection observation protocols.⁴

CONCLUSIONS

To date, there are no validated predictive models or tools to assist clinicians in assessing relative risks of individual patients being considered for SCIT. Given the likely impact of asthma on the risk of severe SRs, it might be possible to develop such a tool that could be validated in a prospective study. To keep the safety of SCIT in perspective, however, severe anaphylaxis is an extremely rare event, and the global benefits of SCIT from the standpoints of reducing morbidity due to allergic asthma and allergic rhinitis and improving quality-of-life outcomes far outweigh the potential risks in most patients. Nevertheless, there are some high-risk patients in whom initiation or continuation of

SCIT may be ill-advised. Clearly, this could include patients with asthma who experience multiple exacerbations that are uncontrolled with optimized pharmacotherapy. Continuation of SCIT is ill-advised in the patient experiencing near-fatal (ie, grade 4) anaphylaxis in response to a prior injection. Establishing rules requiring patients to remain in the injection facility for at least 30 minutes is essential. It is incumbent on facilities administering allergen injections to be fully equipped and fully prepare attending medical staff to promptly recognize and aggressively treat anaphylaxis with epinephrine without hesitation. In the long run, these measures may be the best strategies for improving patient safety.

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