

Letter to the Editor

Factors associated with severe versus mild immunotherapy-related systemic reactions: A case-referent study

To the Editor:

We recently reported first year outcomes (2007-2008) from the American College of Allergy, Asthma & Immunology/American Academy of Allergy, Asthma & Immunology collaborative surveillance study of systemic reactions (SRs) with subcutaneous immunotherapy (SCIT) injections.¹ Allergists reported annual numbers of mild grade 1 SRs (defined as urticaria or upper respiratory symptoms), moderate grade 2 SRs (defined by asthmatic symptoms with or without urticaria, upper respiratory symptoms, or abdominal symptoms), and grade 3 life-threatening anaphylactic reactions in their clinical practices. Of 8502 SRs occurring in allergy practices of 1922 SCIT prescribers, 74% were grade 1, 23% were grade 2, and 3% were grade 3 anaphylactic events. To identify SCIT related practices associated with grade 3 anaphylactic events, we administered an online follow-up questionnaire to a group of practices reporting grade 3 SRs (defined as cases) and compared their responses to practices reporting only grade 1 SRs (controls).

The questionnaire included clinic protocols regarding selection of patients with asthma for SCIT, adjustment of SCIT during peak allergy seasons and after large local or SRs, postinjection observation periods, preinjection screening for asthma control, preparation of patient-specific vials versus shared patient vials, premedication with antihistamines, recommendation of self-administered epinephrine, implementation of Allergen Immunotherapy Practice Parameter recommendations to prevent and treat SRs,² and customary maintenance doses of standardized allergens. A total of 166 respondent practices reporting grade 1 SRs only and 111 respondent practices reporting any grade 3 SRs were approached. Completed evaluable questionnaires were received from 74 allergy practices including 35 clinics reporting grade 3 SRs and 39 clinics reporting only grade 1 SRs.

Practices experiencing grade 3 anaphylactic reactions more frequently reported using high-maintenance dose ranges of house dust mite, defined as 1000 to 1999 allergy units (v 500-999 allergy units or <500 allergy units of Der f 1, Der p 1) versus practices with grade 1 SRs (91.2% vs 64.1%, respectively; $P = .0225$). Respondents with grade 3 SRs reported more frequently administering high target dose ranges of standardized cat extract (2000-4000 biologic allergen units Fel d 1; 62.9% vs 56.4%) and higher dose ranges of standardized grass pollen (2000-4000 biologic allergen units; 74.3% vs 66.7%) than control clinics, although these trends were not significant. Because 1 of the grade 3 respondents and none of grade 1 respondents reported routinely prescribing doses of house dust mite below the recommended range (<500 allergy units), it is unlikely that the significant dosing difference between the latter groups is attributable to subtherapeutic dosing.

As shown in Table I, practices experiencing grade 3 versus grade 1 SRs more frequently reported always or often asking patients to provide personal identifiers before injections (74% vs 56%; $P = .009$), always or often prescribing self-administered epinephrine to patients with asthma on SCIT (74% vs 18%; $P = .006$), always or often instructing patients to premedicate with antiallergic drugs before SCIT (52% vs 21%; $P = .01$),

always or often prescribing and instructing on self-administration of epinephrine to all patients on SCIT (37% vs 18%; $P = .03$), and always or often prescribing and instructing on self-administration of epinephrine in patients with previous SCIT-related SRs (74% vs 56%; $P = .04$).

Although SCIT is effective in treating allergic respiratory disorders, its benefit must be weighed against risks of severe SRs and potentially fatal anaphylaxis. Although fatal reactions to SCIT injections are extremely rare, a published survey in North America estimated that 3.4 fatal events/y occurred between 1990 and 2001 at a rate of 1 per 2,500,000 injections.³ Uncontrolled asthma, dosing errors, SRs after previous injections, administration of injections outside a medical facility, and delay in administration of epinephrine may contribute to fatal SCIT reactions. In response to such reports, updated Immunotherapy Practice Parameters have emphasized specific measures aimed at preventing anaphylaxis and fatal reactions.² These include prescreening of patients with asthma before injections, timely use of epinephrine for treating SRs, and administration of injections exclusively in facilities equipped to treat anaphylaxis. As mentioned, the physician response rates were low, thereby introducing the possibility of reporter bias. As in case-control studies in general, those responding may be more or less likely to have observed severe reactions, and may dwell more on past practices (recall bias). Nevertheless, given the small sample size or limited power, a number of statistically significant differences in responses were observed.

In addition to annually monitoring fatal reactions, secondary aims of this annual surveillance study of SRs to SCIT and skin testing are to evaluate incidence rates of nonfatal SRs of varying severity and define current clinical practices pertaining to SCIT. In this case-control survey, we recruited 2 groups of physician respondents representing allergy practices that experienced either some severe or only mild SRs during the preceding year. We discovered that clinics reporting grade 3 SRs were more likely to use higher maintenance doses of house dust mite, and similar but albeit nonsignificant trends were found for standardized cat and grass pollen allergens. These findings suggest but do not prove that use of higher allergen doses of standardized therapeutic house dust mite extracts could be associated with greater risk of grade 3 SRs. These findings may be consistent with a recent retrospective national survey reporting that the majority of serious near-fatal and fatal SCIT reactions occurred with higher-dose injections from maintenance vials rather than build-up vials.³⁻⁵ There are little if any dose-response data from which to infer the optimally safe dosages of standardized aqueous extracts as has been achieved for certain formulations of sublingual immunotherapy currently being investigated. Thus, larger clinical outcome studies may be required in the future to determine the optimal therapeutic window for various standardized aqueous allergen products.

The only other significant findings differentiating the 2 groups were that clinics reporting grade 3 SRs were more likely than those reporting grade 1 SRs to implement safety measures including obtaining patient identifiers before injections, pretreating with antiallergic drugs, and prescribing epinephrine for high-risk patients (eg, all patients with asthma) or even for all patients receiving SCIT. It is quite possible that those clinicians observing

TABLE I. Summary of survey questions showing significant differences in responses (always, often, sometimes, or never) between a subset of allergy practices reporting severe grade 3 SRs and a subset reporting only mild grade 1 SRs after SCIT injections during 2007 and 2008

Question	Severity of reported SRs	Always	Often	Sometimes	Never	P value
Are patients asked to provide identifiers prior to immunotherapy?	Grade 1	22 (56.4)	0	2 (5.1)	15 (38.5)	.0094
	Grade 3	22 (62.9)	4 (11.4)	5 (14.3)	4 (11.4)	
Are asthmatics prescribed epinephrine for self-administration?	Grade 1	5 (12.8)	2 (5.1)	20 (51.3)	12 (30.8)	.0062
	Grade 3	12 (70.6)	1 (2.9)	21 (60)	1 (2.9)	
Are patients routinely instructed to pre-medicate with antihistamines and/or anti-allergic drugs prior to immunotherapy?	Grade 1	3 (7.7)	5 (12.8)	22 (56.4)	9 (23.1)	.011
	Grade 3	8 (22.9)	10 (28.6)	16 (45.7)	1 (2.9)	
Are patients on SCIT prescribed epinephrine and instructed on self-administration?	Grade 1	5 (12.8)	2 (5.1)	21 (53.9)	11 (28.2)	.0258
	Grade 3	12 (34.3)	1 (2.9)	20 (57.1)	2 (5.7)	
Are patients with prior SCIT systemic reactions prescribed epinephrine and instructed on self-administration?	Grade 1	14 (35.9)	8 (20.5)	10 (25.6)	7 (18.0)	.042
	Grade 3	20 (57.1)	6 (17.1)	9 (25.7)	0	

grade 3 events may have adapted new standards for prescribing self-administered epinephrine as a direct result of concerns about late-onset SRs beginning after the customary 30-minute postinjection observation period. Indeed, in year 2 of this annual surveillance study,⁶ we learned that 14% of SRs started 30 minutes after SCIT injections, although only 3% of these were severe grade 3 SRs. Although the most recent update of the Allergen Immunotherapy Practice Parameters found insufficient evidence to support the routine prescription of emergency epinephrine kits to all patients receiving SCIT, it is clear that more clinical data are needed to determine the impact of this practice on clinical outcomes.⁷ Finally, it is possible that other clinical practices not addressed in this retrospective survey (eg, use of cluster or rush SCIT protocols) could also predict risk of severe SRs.

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