Assessing the safety of subcutaneous immunotherapy dose adjustments

Christopher M. Webber, MD;* and Christopher W. Calabria, MD*

Background: Subcutaneous immunotherapy injections are often dose adjusted owing to late injections, for newly mixed vials after refills, or after systemic reactions (SRs) to reduce the subsequent SR risk. This practice is not strongly evidence based.

Objectives: To analyze the safety of the Wilford Hall Medical Center dose-adjustment schedule.

Methods: A retrospective cohort analysis of a standardized dose-adjustment schedule across 4 years and covering 12,895 injections was performed to analyze the SR rate immediately after dose adjustments for late reactions (1 dose for each week late starting after 2 weeks), for newly mixed vials (a 50% dose reduction), or after a SR (a 10-fold dilution).

Results: Male patients (odds ratio [OR], 1.15; $P < .005$), pediatric patients (OR, 1.19; $P < .01$), and maintenance stage injections (OR, 2.14; $P < .001$) required more dose adjustments for late injections. Maintenance stage injections also experienced more dose adjustments for newly mixed vials (OR, 10.78; $P < .001$). Pediatric patients (OR, 2.15; $P < .002$) and buildup stage injections (OR, 2.38; $P < .005$) were associated with an increased SR frequency and, as a result, required more post-SR dose adjustments. In each scenario, following the dose-adjustment schedule included in this article did not cause an increase in subsequent SRs.

Conclusions: Multiple unique characteristics were found to be associated with the requirement for subcutaneous immunotherapy dose adjustment, and this sample dose-adjustment protocol was not associated with an increased risk of a subsequent SR. The safety of this proposed dose-adjustment protocol should be confirmed in future prospective studies.

Ann Allergy Asthma Immunol. 2010;105:369–375.

INTRODUCTION

To achieve maximal clinical effectiveness, a patient receiving subcutaneous immunotherapy (SCIT) would ideally receive increasing immunotherapy concentrations during buildup until reaching and then continuing the optimal maintenance dose without any interruption of the dosing schedule. However, there are several scenarios in which the practicing allergist will recommend a dose adjustment, including for late injections, for newly mixed vials after refills, and after a systemic reaction (SR). Each scenario shares a similar immunologic and safety concern: administration of a non–dose-adjusted SCIT injection may deliver an allergen concentration greater than what the patient is expected to tolerate, resulting in an SR. The intention of SCIT dose adjustment is presumed, although not proved, to reduce the risk of SRs.

Most practicing allergists have adopted some method of SCIT dose adjustment, likely in an effort to maintain patient safety, and the immunotherapy practice parameter provides a sample dose-adjustment schedule for the allergist's consideration for missed injections during the buildup phase.[1] However, and as expressed in the practice parameter, the practice of dose adjustment is based on anecdotal experience and is not evidence based. Ideally, evidence-based research would provide the practicing allergist with an optimal dose-adjustment strategy that provides a safety margin sufficient to prevent SRs but not so large as to make it difficult to achieve and continue an efficacious maintenance dose. One dilemma in researching this ideal schedule is that the physician would need to deviate from the practice parameter (and arguably standard of care) to create a non–dose-adjusted control population, which may unnecessarily jeopardize patient safety by increasing the risk of anaphylaxis.

In an effort to maintain patient safety and advance toward an evidence-based dose-adjustment schedule, one method of approaching the dilemma is through a 3-step process. First, current dose-adjustment policies should be examined to prove that they sufficiently adjust SCIT concentrations to not cause an increase in SRs. Second, using a safe dose-adjustment policy as a baseline, subsequent studies could be performed with progressively decreased dose-adjustment concentrations to determine whether there is an optimal range between efficiency and safety. Finally, if safety is maintained with minimal dose adjustments, a trial without any dose adjustments can be pursued. Although this is only one method of achieving an evidence-based dose-adjustment schedule, it prioritizes patient safety and can potentially create multiple studies to guide a practicing allergist's clinical experience. Starting this process, the primary purpose of this study was to review the dose-adjustment protocol used at Wilford Hall Medical Center, which has been consistently used for 4 years, and to determine whether the protocol safely reduces SCIT concentrations enough to not cause an increase in SRs. We

Affiliations: * Department of Allergy and Immunology, Wilford Hall Medical Center, Lackland AFB, Texas.

Disclosures: Authors have nothing to disclose.

Received for publication May 4, 2010; Received in revised form September 1, 2010; Accepted for publication September 6, 2010.

doi:10.1016/j.anai.2010.09.003

also analyzed characteristics associated with requiring a dose-adjusted injection.

METHODS

A retrospective cohort analysis of a SCIT-specific electronic medical record (Rosch Immunotherapy, Altoona, Pennsylvania) at a single site was performed. All patients receiving aeroallergen SCIT starting immunotherapy between August 1, 2005, and May 28, 2009, were included in the analysis, and written informed consent was obtained at the time of SCIT enrollment. Patients receiving venom immunotherapy were not included. Baseline demographics included age at first SCIT injection (pediatric, <18 years old), sex, and history of asthma. A history of asthma, as defined in this study, included patients requiring daily inhaled corticosteroids or inhaled corticosteroids + long-acting β_2-agonist medication. All patients receiving SCIT from Wilford Hall Medical Center receive their immunotherapy shots in its clinic. As a result, this study reflects all patients receiving SCIT and not a high-risk subset.

Each patient's immunotherapy kit consisted of three 5-mL buildup vials (1:1,000 to 1:10 vol/vol) and one 10-mL maintenance vial (1:1 vol/vol) using the color and concentration system recommended by the current immunotherapy practice parameter.[1] The maintenance vial for aeroallergen SCIT consisted of 0.5 to 1.0 mL of each allergen taken from the manufacturer's stock vial and corresponded to 1:100 to 1:200 wt/vol. Patients had a mean (SD) of 17.99 (11.31) unique allergens with a mean (SD) volume of 12.56 (6.89) mL. If a patient's immunotherapy kit consisted of more than 10 mL, their total dose was split into multiple vials, with no individual vial exceeding 10 mL. All allergen extracts came from Hollister-Stier Laboratories (Spokane, Washington), and no extract contained aluminum hydroxide. The diluents used when filling the 10-mL maintenance vial or when diluting to a weaker concentration were 0.9% sodium chloride, 0.03% albumin (human), and 0.4% phenol. The buildup stage consisted of the initial SCIT dose of 0.05 mL of the 1:1,000 vol/vol vial through the first maintenance injection of 0.5 mL of the 1:1 vol/vol vial, in 0.1-mL increments. The maintenance stage included all subsequent injections. All the patients were required to attend an immunotherapy orientation class before the first SCIT injection. During this class, patients were informed that the buildup stage consists of a minimum of 1 SCIT injection every 2 weeks through a

Table 1. Dose-Adjustment Schedule (Buildup and Maintenance Stages)

	Dose adjustments
For late injections, time since last injection, d (wk)	
≤14 (<2)	Increase volume per buildup schedule
15–28 (2–4)	Repeat volume of last dose
29–35 (4–5)	Decrease volume by 1 dose
36–42 (5–6)	Decrease volume by 2 doses
43–49 (6–7)	Decrease volume by 3 doses
50–56 (7–8)	Decrease volume by 4 doses
≥57 (>8)	Consult with allergist
For a new vial	Decrease volume by 50%
For a systemic reaction	Decrease by 1 vial (10-fold dilution)

Table 2. Baseline Characteristics and Requirements for SCIT Dose Adjustment

	Injections, No. (N = 12,895)	Late injections			
		On-time injections, No. (%) (n = 11,386)	Late injections, No. (%) (n = 1,509)	OR (95% CI)	*P* value[a]
Patient Demographics					
Sex					
Male	6,031	5,274 (87.4)	757 (12.6)	1.15 (1.05–1.30)	<.005
Female	6,864	6,112 (89.0)	752 (11.0)	0.85 (0.77–0.95)	
Age group					
Pediatric	2,441	2,119 (86.8)	322 (13.2)	1.19 (1.04–1.35)	<.01
Adult	10,454	9,267 (88.6)	1,187 (11.4)	0.84 (0.74–0.96)	
Asthma					
Hx asthma	3,431	3,060 (89.2)	371 (10.8)	NA	<.06
No asthma	9,464	8,326 (88.0)	1,138 (12.0)	NA	
Injection Characteristics					
Stage					
Buildup	8,610	7,843 (91.1)	767 (8.9)	0.47 (0.42–0.52)	<.001[a]
Maintenance	4,285	3,543 (82.7)	742 (17.3)	2.14 (1.92–2.39)	

Abbreviations: CI, confidence interval; Hx, history of; NA, not applicable; OR, odds ratio; SCIT, subcutaneous immunotherapy; SR, systemic reaction.

[a] The *P* values were calculated using χ^2 analysis.

maximum of 2 injections per week separated by at least 2 days, as described in the practice parameter.[1] Maintenance dosing extends SCIT administration to 1 injection per 4-week interval as tolerated. Cluster or rush schedules were not included in this study.

Clinic safety policies and procedures followed those recommended by the practice parameter and included preinjection peak expiratory flow rates for all asthmatic patients, a standard preinjection screening questionnaire, and a mandatory 30-minute wait after all injections.[1] In addition, the Rosch electronic medical record has inherent safety features that prompt the nurse or technician administering the SCIT to scan the patient's vial before giving the injection. This ensures proper identification of the patient and links the patient to his or her vial. On scanning the vial, the nurse is prompted to give the next dose in the injection sequence, minimizing the risk of a dosing error. Approval for this study was obtained from the Wilford Hall Medical Center institutional review board.

Dose-Adjustment Protocol

Table 1 describes the dose-adjustment protocol used at Wilford Hall Medical Center, which is uniformly calculated based on time since the patient's last injection (as opposed to being based on number of days late). For late injections, the protocol reduces a patient's SCIT dose based on a set amount of doses (eg, reduce by 2 doses) and is standardized through 8 weeks late. Patients more than 8 weeks late are adjusted based on their primary allergist's recommendations. A buildup dose is considered late if more than 14 days (ie, ≥15) have passed since the previous injection. A maintenance dose is considered late if more than 28 days have passed since the previous injection. Patients in the maintenance stage who had their dose reduced enough to require an additional buildup injection reverted back to their original buildup schedule.

For injections from a newly mixed vial (due to breakage or maintenance vial refill), the patient's next SCIT dose is reduced by 50%, followed by resumption of the normal buildup schedule. For injections immediately after an SR, a patient's SCIT dose is reduced by 1 vial (a 10-fold dilution), with subsequent resumption of the normal buildup schedule (eg, if the SR occurred at 0.5 mL of the red 1:1 vol/vol vial, the post-SR dose becomes 0.5 mL of the yellow 1:10 vol/vol vial). All dose reductions are additive (eg, a patient who has a new vial and is also late will have his or her next dose reduced by 50% for the new vial and an additional amount based on the time since the last injection). At Wilford Hall Medical Center, SCIT doses are not adjusted based on large local reactions, pollen season, or pollen counts or during periods of exacerbation of allergic rhinitis symptoms.

Reaction Definitions

A local reaction was defined as the presence of erythema measuring at least 5 mm but less than the size of the patient's palm (average adult, 10 cm) measured at 30 minutes. A large local reaction was defined as the presence of erythema larger than the patient's palm measured at 30 minutes. Distinguishing between and recording local and large local reactions at the time of the injection was standard at Wilford Hall Medical Center. An SR included any reaction attributable to SCIT other than a local or large local reaction and was consistent with the World Allergy Organization criteria.[2] All the SRs were directly evaluated, diagnosed, and treated by a team of physicians that included at least 1 allergy/immunology fellow

Table 2. *(Continued)* Baseline Characteristics and Requirements for SCIT Dose Adjustment

First injection of a new vial				First injection after an SR			
Injection from previously mixed vial, No. (%) (n = 12,807)	First injection from new vial, No. (%) (n = 88)	OR (95% CI)	*P* value[a]	Injections not proceeded by SR, No. (%) (n = 12,826)	First injection after SR, No. (%) (n = 69)	OR (95% CI)	*P* value[a]
Patient Demographics							
5,997 (99.4)	34 (0.6)	NA	<.13	6,003 (99.5)	28 (0.5)	NA	<.30
6,810 (99.2)	54 (0.8)	NA		6,823 (99.4)	41 (0.6)	NA	
2,427 (99.4)	14 (0.6)	NA	<.47	2,418 (99.1)	23 (0.9)	2.15 (1.30–3.56)	<.002
10,380 (99.3)	74 (0.7)	NA		10,408 (99.6)	46 (0.4)	0.47 (0.28–0.77)	
3,414 (99.5)	17 (0.5)	NA	<.12	3,408 (99.3)	23 (0.7)	NA	<.21
9,393 (99.2)	71 (0.8)	NA		9,418 (99.5)	46 (0.5)	NA	
Injection Characteristics							
8,596 (99.8)	14 (0.2)	0.09 (0.05–0.16)	<.001	8,553 (99.3)	57 (0.7)	2.38 (1.27–4.42)	<.005
4,211 (98.3)	74 (1.7)	10.78 (6.09–19.13)		4,273 (99.7)	12 (0.3)	0.42 (0.23–0.79)	

and 1 allergy/immunology staff physician. Severity of SRs was not assessed in this article.

Statistical Analysis

Statistical analysis was performed using contingency tables (the Fisher exact test for small sample sizes and the χ^2 test for large sample sizes) through the SPSS/PASW software package (PASW 17; SPSS Inc, Chicago, Illinois). Odds ratios (ORs) with 95% confidence intervals (CIs) achieved statistical significance at $P < .05$.

RESULTS

Baseline Demographics and SR Characteristics

A total of 414 patients (45.7% male, 81.9% adult, and 24.4% asthmatic) received 12,895 injections during the study period. There were 8,610 buildup stage injections (66.8%) and 4,285 maintenance stage injections (33.2%). Overall, 82 SRs were experienced by 66 individual patients (15.9%), resulting in a 0.64% per-injection SR rate. Pediatric patients (29 of 2,441 [1.2%]) had a higher SR rate than did adults (53 of 10,454 [0.5%]) (OR, 2.36; 95% CI, 1.50–3.72; $P < .001$). In addition, there were more SRs in the buildup stage (67 of 8,610 [0.8%]) than in the maintenance stage (15 of 4,285 [0.4%]) (OR, 2.23; 95% CI, 1.27–3.91; $P < .004$). As a result of these 2 findings, the dose-adjustment safety analysis was subdivided into separate buildup and maintenance categories, and age was analyzed within each group to ensure that this was not a confounding variable. There was no significant difference in the number ($P < .47$) or volume ($P < .19$) of allergens between the SR and non-SR groups.

Baseline Characteristics Requiring Dose Adjustment

We initially analyzed specific baseline characteristics associated with SCIT dose adjustment (Table 2). Of the 12,895 total injections, 1,509 (11.7%) were late. Male patients (757 of 6,031 [12.6%]) were more likely to have late injections than were female patients (752 of 6,864 [11.0%], $P < .005$). Also, pediatric patients (322 of 2,441 [13.2%]) were more likely to have a late injection than were adults (1,187 of 10,454 [11.4%], $P < .01$). Asthma was not associated with an increased risk of late injections. Maintenance stage injections (742 of 4,285 [17.3%]) were almost twice as likely to be late than were buildup stage injections (767 of 8,610 [8.9%], $P < .001$). The maintenance stage was also the only baseline characteristic associated with injections from a newly mixed vial, occurring in 74 (1.7%) of the maintenance stage's 4,285 injections and in only 14 (0.2%) of the buildup stage's 8,610 injections ($P < .001$).

Regarding SCIT dose adjustment after an SR, 57 of the 66 patients (86.4%) experiencing SRs continued receiving immunotherapy and 9 (13.6%) chose to stop immunotherapy. Because some patients had multiple SRs, 69 individual post-SR SCIT injections were reviewed. Pediatric patients (23 of 2,441 [0.9%]) had more injections immediately after an SR than did adult patients (46 of 10,454 [0.4%], $P < .002$). Buildup stage injections (57 of 8,610 [0.7%]) were also more likely to follow an SR than were maintenance stage injections (12 of 4,285 [0.3%], $P < .005$). These results likely reflect the earlier finding that pediatric patients and buildup stage injections were significantly more likely to experience an SR.

Safety of Dose Adjustment

Buildup stage. A total of 767 of the 8,610 SCIT buildup stage injections were late injections requiring dose adjustment (Table 3). There were 2 subsequent SRs (0.3%) in the dose-adjusted injections compared with 65 SRs (0.8%) found in the on-time injections. Dose adjustment for late injections was not more likely to cause a subsequent SR ($P < .09$). A subgroup analysis of the specific time-adjustment periods showed that most late injections were 2 to 4 weeks late (611 injections [79.7%]). Although the small sample size may limit the applicability of the subgroup analysis, the Fisher exact test did not show that any single time-adjustment period was more likely to have an SR.

Only 14 buildup stage injections required dose adjustment due to being the first injection from a newly remixed vial. There were no SRs in this dose-adjusted group, and the Fisher exact test analysis based on expected values showed that newly mixed vial dose adjustment was not more likely to cause a subsequent SR ($P > .99$).

There were 57 dose-adjusted buildup stage injections immediately after an SR, resulting in 1 new SR (1.8%). Compared with the 66 SRs (0.8%) immediately after the non–dose-adjusted buildup injections, there was no significant increased risk of a second SR after dose adjustment from a previous SR ($P = .36$).

Maintenance stage. Table 4 details the safety of dose adjustments during the maintenance stage of SCIT. Dose adjustments were required for 742 late injections, resulting in 1 subsequent SR (0.1%). There were 14 SRs (0.4%) in the on-time, non–dose-adjusted injections. Similar to the buildup stage, the maintenance stage's dose adjustment for late injections was not more likely to cause an SR than were the on-time, non–dose-adjusted injections ($P < .49$). A breakdown of specific time-adjusted injections was also performed, although the low sample size limits the application of these data.

The maintenance stage had 74 injections from a newly mixed vial that required dose adjustment, resulting in 1 subsequent SR (1.4%). This was not significant compared with the 14 SRs (0.3%) after the 4,211 non–dose-adjusted maintenance stage injections ($P = .23$).

Finally, 12 maintenance stage injections immediately followed an SR and required dose adjustment. There were no additional SRs in the dose-adjusted group. Compared with the 15 SRs (0.4%) from the 4,273 non–dose-adjusted injections, the dose-adjustment protocol after an SR was not associated with an increased risk of SRs ($P > .99$).

Table 3. Safety of the Dose-Adjustment Schedule During the Buildup Stage

	Injections, No. (%) (N = 8,610)		*P* value
	No. SRs (n = 8,543)	SRs (n = 67)	
Dose adjustments for time since last injection			.09[a]
On-time injections (no dose adjustment) (n = 7,843)	7,778 (99.2)	65 (0.8)	
Late injections (dose adjustment) (n = 767)			
All time-adjusted injections	765 (99.7)	2 (0.3)	
Specific time-adjusted injections, wk			
2–4	610 (79.7)	1 (50)	.09[b]
4–5	63 (8.2)	1 (50)	.42[b]
5–6	32 (4.2)	0	>.99[b]
6–7	14 (1.8)	0	>.99[b]
7–8	7 (0.9)	0	>.99[b]
>8	39 (5.1)	0	>.99[b]
Dose adjustments for new vials (remixed from stock allergen owing to expiration or vial breakage)			>.99[b]
Injections from previously mixed vials (n = 8,596)	8,529 (99.8)	67 (0.8)	
First injections from remixed new vials (n = 14)	14 (100)	0	
Dose adjustments after SRs			.36[b]
Injections not preceded by SR (n = 8,553)	8,487 (99.3)	66 (0.7)	
First injection after SR (n = 57)	56 (98.2)	1 (1.8)	

Abbreviation: SR, systemic reaction.
[a] *P* value was calculated using χ^2 analysis.
[b] *P* values were calculated using the Fisher exact test.

Table 4. Safety of the Dose Adjustment Schedule During the Maintenance Stage

	Injections, No. (%) (N = 4,285)		*P* value
	No SRs (n = 4,270)	SRs (n = 15)	
Dose adjustments for time since last injection			<.49[a]
On-time injections (no dose adjustment) (n = 3,543)	3,529 (99.6)	14 (0.4)	
Late injections (dose adjustment) (n = 742)			
All time-adjusted injections	741(99.9)	1 (0.1)	
Specific time-adjusted injections, wk			
2–4	306 (41.3)	0	.62[b]
4–5	284 (38.3)	0	.62[b]
5–6	67 (9.0)	0	>.99[b]
6–7	32 (4.3)	0	>.99[b]
7–8	20 (2.7)	0	>.99[b]
>8	32 (4.3)	1 (100)	.14[b]
Dose adjustments for new vials (remixed from stock allergen owing to expiration or vial breakage)			.23[b]
Injections from previously mixed vials (n = 4,211)	4,197 (99.7)	14 (0.3)	
First injections from remixed new vials (n = 74)	73 (98.6)	1 (1.4)	
Dose adjustments after SRs			>.99[b]
Injections not preceded by SR (n = 4,273)	4,258 (99.6)	15 (0.4)	
First injection after SR (n = 12)	12 (100)	0	

Abbreviation: SR, systemic reaction.
[a] *P* value was calculated using χ^2 analysis.
[b] *P* values were calculated using the Fisher exact test.

DISCUSSION

Although SCIT was empirically adopted based on the observations of Noon and Freeman, Cooke's grass pollen immunotherapy research 1 year later advanced the scientific acceptance of SCIT's efficacy.[3] Since then, SCIT has become recognized as an evidence-based therapeutic modality for allergic rhinitis, allergic asthma, and venom hypersensitivity.[1] Similarly, multiple evidence-based studies[4–12] have tried to identify risk factors associated with SRs. However, one area that remains without a clear evidence basis is the practice of SCIT dose adjustments.

Three common dose-adjustment scenarios include for late injections, after starting a newly mixed vial, and after experiencing an SR. Justification for late injection dose adjustment stems from the concern that the patient may have lost some of the immunologic tolerance conferred by previous SCIT injections. As a result, administration of a non–dose-adjusted SCIT injection may present a relatively large allergen amount, causing an SR. Similar concerns have been raised and found clinically significant with interruptions in treatment after a penicillin or aspirin desensitization.[13] In the second scenario, justification for dose adjusting newly mixed vials is the concern that the patient's expiring allergen vial's potency may have degraded below its stock precursor. As a result, administration of a non–dose-adjusted injection from the higher-potency newly mixed vial may result in an SR. Finally, for dose adjustments after an SR, the concern is that the inciting SCIT dose's allergen concentration may have been too high for the patient's stage of immunologic tolerance, and administration of the same or a greater dose on the next visit could cause another SR. In all 3 scenarios, the intention of SCIT dose adjustment is to improve patient safety by reducing the risk of causing a subsequent SR. For this reason, the immunotherapy practice parameter provides a sample late dose–adjustment protocol and also adds considerations for new vial and post-SR dose adjustments.[1]

None of these recommendations have a strong evidence base. Only 1 recent letter to the editor[14] has been published addressing SCIT dose adjustments, and it was an observational study reviewing the 16 different late injection dose-adjustment protocols at the author's institution. The author's conclusion was that there were marked differences among the practicing allergists, and the use of inconsistent dose-adjustment schedules may result in an increase in medical errors.[14] The present study begins to reconcile the need for an evidence-based dose-adjustment schedule and the need for a more standardized dose-adjustment protocol by analyzing the 4-year experience at Wilford Hall Medical Center using a standard dose-adjustment protocol (Table 1) for 12,895 SCIT injections.

We first examined the population at risk for needing dose adjustments. Male patients and pediatric patients (age <18 years) were more likely to be late for an injection, as were patients in the maintenance stage. We cannot speculate on the sex differences, but the pediatric finding may reflect this population's difficulty with school or transportation requirements, and the maintenance stage finding may be due to difficulty remembering a monthly vs a weekly schedule. The maintenance stage was also associated with more injections from newly mixed vials. This finding should be expected considering that new vials are most often mixed when the maintenance vial expires after 12 months. Finally, in this population, SRs were more likely to occur in pediatric patients and during the buildup stage, and, as a result, these patients were also more likely to require a post-SR dose adjustment.

The primary purpose of this study was to assess the safety of the dose-adjustment protocol used at Wilford Hall Medical Center. To this end, there were no statistically significant increases in SRs using any component of this study's dose-adjustment protocol. Dose-adjusted late injections had a lower SR rate than did non–dose-adjusted injections during the buildup and maintenance stages. The SR rate was also lower for newly mixed vial dose-adjusted injections during the buildup stage and post-SR dose-adjusted injections during the maintenance stage compared with their respective non–dose-adjusted injections. However, the SR rate was higher for newly mixed vial dose-adjusted injections during the maintenance stage and for post-SR dose-adjusted injections during the buildup stage than for non–dose-adjusted injections. These values were not statistically significant and may reflect the higher number of newly mixed vials associated with maintenance stage injections and the higher number of SRs during buildup stage injections.

Note that we cannot state that this dose-adjustment schedule is the optimal dose-adjustment schedule or even that dose adjustments are necessary. Ideally, using this study as a baseline, additional research can now be performed to determine whether there is additional safety from larger dose adjustments, whether similar safety can be maintained with smaller dose reductions, and whether dose adjustments are even necessary.

There are several limitations of this study. First, by nature of its design as a retrospective analysis of a standardized dose-adjustment protocol, the strength of the consistency is balanced by the limitation that we can analyze only the outcome of the current dose-adjustment protocol and cannot compare multiple different dose-adjustment strategies. Second, although this is the largest study to date on dose-adjustment protocols, we are limited by a small sample size, particularly in specific intervals of late injections. Finally, at Wilford Hall Medical Center, we do not dose adjust owing to pollen season or exacerbation of underlying allergic rhinitis and, thus, cannot comment on other possible components of dose adjustment.

In summary, male and pediatric patients and maintenance stage injections were most likely to require dose adjustments owing to late injections, maintenance stage injections were most likely to require newly mixed vial dose adjustments and, pediatric patients and buildup stage injections experienced the most SRs and, as a result, required post-SR dose adjustments. In each scenario, following the dose-adjustment schedule included herein did not cause an increase in subsequent SRs. We hope that this study encourages discussion of a more standardized dose-adjustment protocol and that this study's protocol may be used as a safe starting point for future trials. In time, subsequent studies should be performed comparing different dose-adjustment schedules to determine whether there is an optimal balance between efficacy and safety.

REFERENCES

1. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol.* 2007;120:S25–S85.
2. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol.* 2010;125:569–574, 574.e1–574.e7.
3. Finegold I. Immunotherapy historical perspective. *Ann Allergy Asthma Immunol.* 2001;87:3–4.
4. Lin MS, Tanner E, Lynn J, Friday GA Jr. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. *Ann Allergy.* 1993;71:557–562.
5. Ragusa VF. Non-fatal systemic reactions to subcutaneous immunotherapy: a 20-year experience comparison of two 10-year periods. *Eur Ann Allergy Clin Immunol.* 2004;36:52–55.
6. Cox L. Allergen immunotherapy and asthma: efficacy, safety, and other considerations. *Allergy Asthma Proc.* 2008;29:580–589.
7. Moreno C. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy.* 2004;34:527–531.
8. Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. *Allergy Asthma Proc.* 2008;29:400–405.
9. Schiappoli M, Ridolo E, Senna G, et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy.* 2009;39:1569–1574.
10. Tankersley MS. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol.* 2000;106:840–843.
11. Tinkelman DG. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol.* 1995; 95:8–14.
12. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. *Clin Exp Allergy.* 2006;36:254–260.
13. Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc.* 2004;25:161–164.
14. Montgomery JR. The need for standardizing the aeroallergen immunotherapy missed-dose adjustment protocol [letter]. *Allergy Asthma Proc.* 2008;29:425–426.

Requests for reprints should be addressed to:
Christopher M. Webber, MD
Wilford Hall Medical Center
59 MDOS/SGO5A
2200 Bergquist Dr, Ste 1
Lackland AFB, TX 78236-9908
E-mail: christopher.m.webber@gmail.com