

Letter

THE CITIES STUDY: CONVENTIONAL IMMUNOTHERAPY-INVESIGATING EXISTING SCHEDULES

To the Editor: The Joint Task Force on Practice Parameters in 2010 reaffirmed that immunotherapy is an efficacious and safe modality in the treatment of allergic rhinoconjunctivitis, allergic asthma, and insect allergy.¹ Immunotherapy schedules can be administered in a variety of ways using numerous conventional or accelerated schedules. Conventional subcutaneous immunotherapy (SCIT) is defined as a build-up phase of once- to twice-weekly visits for administration of allergen extracts during which patients typically receive a single injection per visit.² The duration of the build-up phase is dependent on the physician's prescription schedule and patient tolerance and adherence. The maintenance phase begins when the optimal therapeutic dose is achieved.

To our knowledge, the current literature is absent of any study comparing systemic reaction (SR) rates with one conventional SCIT schedule vs another. The objectives of this study were to use this department's existing schedules to (1) identify all potential SCIT schedules; (2) determine the frequency of schedules used; and (3) define the SR rate in a single-site, busy outpatient allergy department using the usual SCIT build-up schedules.

This retrospective study used an electronic medical record called Rosch immunotherapy. Four years of information was evaluated from August 2005 through May 2009. A mathematical model was used to determine the number of valid schedules and the number of injections accompanying these schedules. Institutional review board

approval for this study was obtained by the Wilford Hall Medical Center. A color-coded and labeled dilution, 4-vial immunotherapy kit, including 1:1 (vol/vol) red, 1:10 (vol/vol) yellow, 1:100 (vol/vol) blue, and 1:1,000 (vol/vol) green, was used. The build-up schedule options included 5 potential dosing schedules to progress through each immunotherapy vial as indicated in Table 1. When writing the immunotherapy prescription for a 4-vial kit, a physician selected the schedule (ie, A, B, C, D, or E), which then guided the build-up within each particular vial (ie, green, blue, yellow, and red). For example, if a physician selected an ABCD schedule, an A schedule (4-injection build-up) would be used for the green vial, a B schedule (6-injection build-up) for the blue vial, a C schedule (7-injection build-up) for the yellow vial, and a D schedule (9-injection build-up) for the red vial. Thus, an ABCD schedule would result in a total of 26 injections to build up to a maintenance dose of 0.5 mL of the 1:1 (vol/vol) red vial. These are the typical schedule options used in our previously reported studies.^{3,4}

A total of 70 potential build-up schedules using a 4-vial immunotherapy kit were mathematically calculated as possible build-up schedules. Among the 70 schedule combinations available to reach a maintenance dose, the scope of injections ranged from 16, using an AAAA schedule, to 44 injections, using an EEEE schedule.

Three schedules (ABBC, 23 injections; AACD, 24 injections; and ABCD, 26 injections) constituted 76.2% of the schedules used during this period. A total of 427 patients receiving build-up phase immunotherapy were reviewed.

The SR rate per total number of injections among the 3 most used schedules was not statistically significant. The total number of build-up phase injections was 10,532. The number of SRs was 54 (42 acute and 12 delayed). The SR rate during this period was 0.51% per immunotherapy injections (54/10,532). A SR, for the purpose of this study, included any reaction attributable to SCIT other than a local or large local reaction. This definition included rhinitis, diffuse urticaria or erythema, generalized pruritus and angioedema, and respiratory, gastrointestinal, or cardiovascular signs or symptoms.

Disclosures: Authors have nothing to disclose.

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doi:10.1016/j.anai.2011.03.015

Table 1. Build-up Schedules^a

Schedule				
A (4 injections)	B (6 injections)	C (7 injections)	D (9 injections)	E (11 injections)
0.05 mL	0.05 mL	0.05 mL	0.05 mL	0.05 mL
0.15 mL	0.1 mL	0.07 mL	0.07 mL	0.07 mL
0.25 mL	0.2 mL	0.1 mL	0.1 mL	0.1 mL
0.5 mL	0.3 mL	0.2 mL	0.15 mL	0.15 mL
	0.4 mL	0.3 mL	0.2 mL	0.2 mL
	0.5 mL	0.4 mL	0.25 mL	0.25 mL
		0.5 mL	0.3 mL	0.3 mL
			0.4 mL	0.35 mL
			0.5 mL	0.4 mL
				0.45 mL
				0.5 mL

^a Example of the ABCD build-up schedule: 1:1,000 (vol/vol) green (A: 0.05 mL, 0.15 mL, 0.25 mL, 0.5 mL), 1:100 (vol/vol) blue (B: 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL), 1:10 (vol/vol) yellow (C: 0.05 mL, 0.07 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL), and 1:1 (vol/vol) red (D: 0.05 mL, 0.07 mL, 0.1 mL, 0.15 mL, 0.2 mL, 0.25 mL, 0.3 mL, 0.4 mL, 0.5 mL).

Table 2. Systemic Reaction (SR) Symptoms

	SR characterizations, No. (%)			Example schedules, No. (%)		
	Total SR (n = 54)	Acute SR (n = 44)	Delayed SR (n = 10)	ABBC ^a (n = 17)	ABCD ^b (n = 8)	AACD ^c (n = 6)
Symptoms						
Naso-ocular	14 (26)	12 (27)	2 (20)	4 (24)	4 (50)	1 (17)
Pruritus	28 (52)	22 (50)	6 (60)	11 (65)	1 (13)	2 (33)
Flushing	17 (31)	13 (30)	4 (40)	7 (41)	2 (25)	2 (33)
Hives	13 (24)	8 (18)	5 (50)	6 (35)	1 (13)	2 (33)
Angioedema	4 (7)	3 (7)	1 (10)	1 (6)	0	1 (17)
Throat pruritus	11 (20)	9 (20)	2 (20)	3 (18)	1 (13)	2 (33)
Headache	1 (2)	1 (2)	0	0	0	1 (17)
Dyspnea	6 (11)	6 (14)	0	1 (6)	3 (38)	0
Cough	15 (28)	12 (27)	3 (30)	5 (29)	3 (38)	1 (17)
Nausea	5 (9)	4 (9)	1 (10)	3 (18)	0	1 (17)
Dizziness	5 (9)	4 (9)	1 (10)	2 (12)	1 (13)	1 (17)
Chest tightness	11 (20)	11 (25)	0	4 (24)	1 (13)	2 (33)
Globus	4 (7)	4 (9)	0	3 (18)	0	3 (50)
Wheezing	4 (7)	4 (9)	0	1 (6)	0	0
Chest pain	1 (2)	1 (2)	0	1 (6)	0	0
Other ^d	2	2	0	0	0	0
WAO category						
Grade 1	25 (46)	20 (45)	5 (50)	6 (35)	4 (50)	2 (33)
Grade 2	29 (54)	24 (55)	5 (50)	11 (65)	4 (50)	4 (66)

Abbreviation: WAO, World Allergy Organization.

Table 2 reports the distribution of SRs during this period. Overall, 25 of 54 (46%) of the SRs were grade 1 reactions and 29 of 54 (54%) were grade 2 reactions per the World Allergy Organization SCIT systemic reaction grading system.⁵ All acute SRs were directly evaluated, diagnosed, and treated by a team of physicians that included at least 1 allergy/immunology fellow and 1 allergy/immunology staff member. A reaction was classified as acute if it occurred within the first 30 minutes and presented during the in-clinic wait time. A reaction was classified as delayed if it occurred after 30 minutes and was reported by the patient either when the patient returned to the clinic for treatment or at the next SCIT visit as identified by a preinjection screening questionnaire.

Because of the retrospective nature of the study, we were unable to determine whether the 3 most used schedules (ABBC, 23 injections; AACD, 24 injections; and ABCD, 26 injections) were safer than all other schedules used. Given that most patients (76.2%) were on a schedule consisting of a 23-, 24-, or 26-injection build-up schedule, it would be anticipated that these 3 schedules would have similar SR rates. The SR rate reported in this study is similar to Stewart and Lockey's review, which reported that the incidence of SR rates with SCIT build-up schedules ranged from 0.05% to 3.2% of injections and 0.84% to 46.7% of patients (mean, 12.92%; SD, 10.8%).⁶

Adherence to SCIT is adversely affected by patient inconvenience and cost.⁷⁻⁹ If proven to be as safe or safer, shorter SCIT schedules may help increase patient adherence without sacrificing patient safety and could aid in making this form of treatment more affordable. We found that 23- to 26-injection build-up schedules were the most popular among our physicians. The SR rate during a 4-year period was 0.51% of immunotherapy injections. Prospective

studies need to be conducted to determine safety and adherence among various conventional SCIT schedules.

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