



Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy



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ARTICLE INFO

Article history:

Received for publication April 12, 2016.

Received in revised form July 21, 2016.

Accepted for publication September 6, 2016.

ABSTRACT

Background: Given the choice of standard, cluster, and rush build-up for aeroallergen immunotherapy, standard-build immunotherapy has generally been preferred because of a perceived high rate of systemic reactions (SRs) associated with cluster and rush immunotherapy.

Objective: To characterize the incidence of SRs during standard, cluster, and rush build-up immunotherapy in an allergy practice during a 5-year period.

Methods: A retrospective review was conducted among patients receiving standard-build, 8- to 10-step cluster, or 2-day rush immunotherapy from January 1, 2010, through December 31, 2014, at Family Allergy & Asthma clinics in Louisville, Kentucky. Investigators excluded reactions that occurred during skin prick testing, venom immunotherapy, and not-true SRs, and identified the build-up method, age, sex, date of reaction, vial concentration, and presence of asthma. Per-shot and per-patient incidence of SRs was computed from these data.

Results: During our review period, 2,549,643 injections were administered to 11,982 patients. Per-shot incidence of SR was 0.01%, 0.06%, and 0.33% for standard, cluster, and rush immunotherapy, respectively; per-patient incidence of SR was 2.84%, 2.52%, and 11.86% for standard, cluster, and rush immunotherapy, respectively. A total of 42% of SRs were grade 1, 43% were grade 2, 12% were grade 3, and 3% were grade 4. No fatalities were reported. A total of 70% of total SRs, 75% of cluster SR, and 55% of rush SR occurred in females, with an emergent peak in SR from May to October.

Conclusion: Compared with previously published rates, we observed a decrease in the incidence of SR for standard, cluster, and rush immunotherapy, with peak seasonality from May to October and a female predominance.

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Introduction

The systemic reaction (SR) rate during subcutaneous immunotherapy is of critical importance to any practicing allergist. On the basis of previous studies, SRs have occurred after 0.026% to 0.37% of subcutaneous injections (1.8%–7.4% of patients) during standard-build aeroallergen immunotherapy,¹ after 0.15% to 3.3% of injections (10.9% of patients) during cluster immunotherapy,² and in 1.3% of injections (28% of patients) during rush immunotherapy.³ Given the choice of standard, cluster, and rush build-up for aeroallergen immunotherapy, standard-build immunotherapy has generally been preferred in part because of a perceived unacceptably high rate of SRs associated with cluster and rush immunotherapy.

Despite the natural appeal of rapid-build immunotherapy because of the increased convenience it confers to patients,⁴ many allergy practices have yet to offer rush immunotherapy.

Family Allergy & Asthma is a large, multicentered allergy practice established in Louisville, Kentucky, in 1979. Its 26 office locations provide allergy care for greater Louisville, Lexington, and various additional Kentucky and southern Indiana communities. From 2010 to 2014, approximately 2.5 million immunotherapy injections were provided at Family Allergy & Asthma practices. As one of the largest private allergy practices with a fundamental interest in research, it championed the safe and effective implementation of cluster and rush immunotherapy schedules as an alternative for patients desiring to expedite their build to maintenance. In one of the first studies comparing standard, cluster, and rush-build immunotherapy offered at the same practice, we seek to characterize the 5-year incidence of SR associated with each of these build-up methods.

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Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.09.005>

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Methods

A retrospective review was conducted among patients receiving standard-build, 8- to 10-step cluster, or 2-day rush immunotherapy from January 1, 2010, through December 31, 2014, at Family Allergy & Asthma offices. Before every injection, patients are screened for a history of reactions to previous injections or any recent asthma symptoms. Patients are observed for a period of 30 minutes after each injection to monitor for immediate SR before being released home. Patients receiving rush build-up immunotherapy are monitored for 2 hours after their last injection each day. Any SRs are recorded on standardized SR flow sheets by the treating nurse and physician. The data recorded include patient demographic information, symptoms categorized by system, vital signs (initially, then at 5, 10, 15, and 30 minutes), and medications or adjunctive treatments given (oxygen, intravenous fluids). The back side of the flow sheet includes pertinent history, such as asthma, β -blocker use, and recent exposures, as well as grading of the SR by the treating health care professional and changes made to the treatment plan. Reactions are graded in accordance with the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.¹ Late reactions are recorded when self-reported, and a SR flow sheet is generated with appropriate changes to treatment. Patients experiencing a SR are routinely followed up by telephone the following day.

The SRs were retrospectively verified by the investigators to exclude reactions occurring during skin prick testing, venom immunotherapy, and not-true SRs, and to identify build-up method, age, sex, date of reaction, vial concentration, and presence of asthma. Per-shot and per-patient incidences of SRs were estimated from extracted electronic medical record data and known numbers of cluster and rush patients. The rates of SRs based on sex for each build-up method were calculated using the known number of SRs for males and females along with estimates from the electronic medical record of the total number of males and females receiving each type of build-up. Sex comparisons were calculated using a Fisher exact test, and $P < .05$ was considered statistically significant.

Patients undergoing standard-build immunotherapy require approximately 30 to 40 injection visits to reach maintenance. Those patients starting cluster immunotherapy receive premedication

with 20 mg of prednisone, H₁-antihistamine, and 10 mg of montelukast before each of their clustered injections. Recipients of rush immunotherapy are premedicated with 40 mg of prednisone, H₁-antihistamine, H₂-antihistamine, and 20 mg of montelukast. Although previously published studies have not supported the routine use of 20 mg of montelukast,⁵ the higher dose of montelukast was selected for rush premedication based on authors' expectation for increased mast cell activation during anaphylaxis and the notion that the 10-mg dose has been carried forth after trials that used end points for alternative applications, including rhinitis⁵ and asthma,⁶ instead of immunotherapy premedication. The rush protocol was designed by Family Allergy & Asthma physicians after a thorough review of previously published protocols and discussions with physicians with prior clinical experience. The protocol underwent slight iterative changes since its inception in 2011. Figure 1 gives illustrative details regarding cluster and rush-build schedules. Figure 2 illustrates typical allergen dose at maintenance used by Family Allergy & Asthma physicians compared to the probable effective dose range in the immunotherapy practice parameter.⁷

A detailed protocol describing the above review was submitted to the University of Louisville Institutional Review Board and was accepted on October 13, 2015.

Results

A total of 2,549,643 build-up and maintenance injections provided at Family Allergy & Asthma clinics were analyzed from January 1, 2010, through December 31, 2014, of which 2,398,491 (94%) occurred during standard-build immunotherapy or maintenance after standard-build immunotherapy, 144,760 (5.7%) occurred during cluster-build immunotherapy or maintenance after cluster-build immunotherapy, and 6,372 (0.2%) occurred during rush-build immunotherapy or maintenance after rush-build immunotherapy. A total of 11,982 patients received injections during this timeframe, with 9,229 receiving standard-build immunotherapy (77%), 2,576 receiving cluster-build immunotherapy (21.5%), and 177 receiving rush-build immunotherapy (1.5%). The total number of injections provided increased annually during this period.

Aeroallergen Immunotherapy Rapid Build Schedules							
Cluster ¹			2-Day Rush ²				
Visit	Concentration	Dosing	Concentration	Day 1	Concentration	Day 2	
1	1:10,000/1:1,000	.1,.2,.4/.1	1:100,000	.25	1:10	.10	
2	1:1,000/1:100	.2,.4/.1	1:100,000	.50	1:10	.25	
3	1:100/1:10	.2,.4/.07	1:10,000	.25	1:10	.50	
4	1:10	.1,.15,.25	1:10,000	.50	1:1	.10	
5	1:10	.35/.5	1:1,000	.25	1:1	.25	
6	1:1	.07,.1	1:1,000	.50	1:1	.50	
7	1:1	.15,.2	1:100	.10			
8	1:1	.3,.4	1:100	.25			
9	1:1	.5	1:100	.50			
			1:10	.10			
			1:10	.25			
			1:10	.50			

¹Premedication (90 min. prior): Prednisone 20 mg, Montelukast 10 mg, H-1 Antihistamine
²Premedication (90 min. prior): Prednisone 40 mg, Montelukast 20 mg, H-1 Antihistamine, H-2 Antihistamine

Figure 1. Build-up schedules used by Family Allergy & Asthma for cluster and rush immunotherapy.

Antigen	Recommended Dose [†]	Maintenance Dose [‡]
Cat	1,000-4,000 BAU	1,000 BAU
Dog	15 mcg Can f 1	About 13 mcg Can f 1
Dust Mite	500-2,000 AU	1,000 AU
Tree	1:100-1:200 W/V	About 1:200 W/V
Pasture Grass	1,000-4,000 BAU	1,000 BAU
Bermuda	300-1,500 BAU	100 BAU
Ragweed	6-12 AgE	3-6 AgE

[†]Cox, Linda, et al. "Allergen immunotherapy: a practice parameter third update." *Journal of Allergy and Clinical Immunology* 127.1 (2011): S1-S55.
[‡]Family Allergy and Asthma dosing

Figure 2. Maintenance doses for common allergens used at Family Allergy & Asthma for all methods of immunotherapy.

A total of 411 SRs were logged from January 1, 2010, through December 31, 2014. A total of 307 of 411 SRs (74.7%) occurred during standard immunotherapy (build-up and maintenance), with a per-patient incidence of 2.8% and a per-shot incidence of 0.01%. A total of 83 of 411 reactions (20.2%) occurred during cluster immunotherapy (build-up and maintenance), with a per-patient incidence of 2.5% and a per-shot incidence of 0.06%. A total of 21 of 411 reactions (5.1%) occurred during rush immunotherapy (build-up and maintenance), with a per-patient incidence of 11.9% and a per-shot incidence of 0.33%. See Table 1 for detail. Most SRs (87%) occurred during build-up, with most of these occurring in the yellow or red vials. The percentage of reactions graded 1 through 5 is represented across each build-up method in Figure 3. Notably, no grade 5 reactions were reported. Figure 4 shows the annual per-shot incidence.

Seasonal peaks in SRs emerged from May to October, a trend that decreased with increasingly rapid build-up schedules (Fig 5). Females outnumbered males in total number of SRs, comprising 69% of the standard-build reactions ($P < .001$), 75% of the cluster-build reactions ($P < .05$), and 52% of the rush-build reactions ($P = .80$). Approximately 57% of all patients undergoing aeroallergen immunotherapy were female. For those patients experiencing SRs, approximately half were previously diagnosed with asthma.

Discussion

In a recent systematic review, the SR incidence has been quoted as 0.05% to 3.2%, 0.15% to 3.3%, and 2.6% to 36.8% per injection for standard, cluster, and rush aeroallergen immunotherapy, respectively.⁸ SRs during aeroallergen immunotherapy at Family Allergy & Asthma practices occurred less frequently than these historical per-shot norms for standard, cluster, and rush immunotherapy. A number of different reasons likely help to account for this difference. First, throughout more than 35 years of clinical experience, the immunotherapy protocol was refined through internal quality

Table 1
Summary of Systemic Reaction Incidence by Build-up Method

Variable	Standard ^a	Cluster ^a	Rush ^a	Total
Injections, No. (%)	2,398,491 (94)	144,760 (5.7)	6,372 (0.2)	2,549,643 (100)
Patients, No. (%)	9,229 (77)	2,576 (21.5)	177 (1.5)	11,982 (100)
SRs, No. (%)	307 (74.7)	83 (20.2)	21 (5.1)	411 (100)
Per-patient incidence, %	2.8	2.5	11.9	
Per-injection incidence, %	0.01	0.06	0.33	

^aIncludes build-up and maintenance after build-up immunotherapy.

Systemic Reaction Severity Versus Aeroallergen Build-Up Method				
Grade	Standard ^o (n=307)	Cluster ^o (n=83)	Rush ^o (n=21)	Total ^Δ (n=411)
1	38%	51%	62%	42%
2	46%	37%	29%	43%
3	13%	11%	4%	12%
4	3%	1%	4%	3%
5	0%	0%	0%	0%

^oPercentages for Standard, Cluster, and Rush denote percentage of World Allergy Organization Grade 1-5 systemic reactions observed for each respective method of immunotherapy build-up
^ΔPercentages for Total denote percentage of World Allergy Organization Grade 1-5 systemic reactions observed across all methods of immunotherapy build-up

Figure 3. World Allergy Organization grade of systemic reactions during standard, cluster, and rush immunotherapy at Family Allergy & Asthma.

improvement measures, which incorporated practice-based improvement ideas, patient comments, and practitioners' successes and failures experienced in everyday practice. As such, immunotherapy methods and protocols were actively scrutinized and modified as deemed necessary. Before receiving an injection, every patient is screened for recent asthma symptoms and previous reactions to their injections. Second, a lower incidence of SRs has been achieved through the use of rapid-build premedication

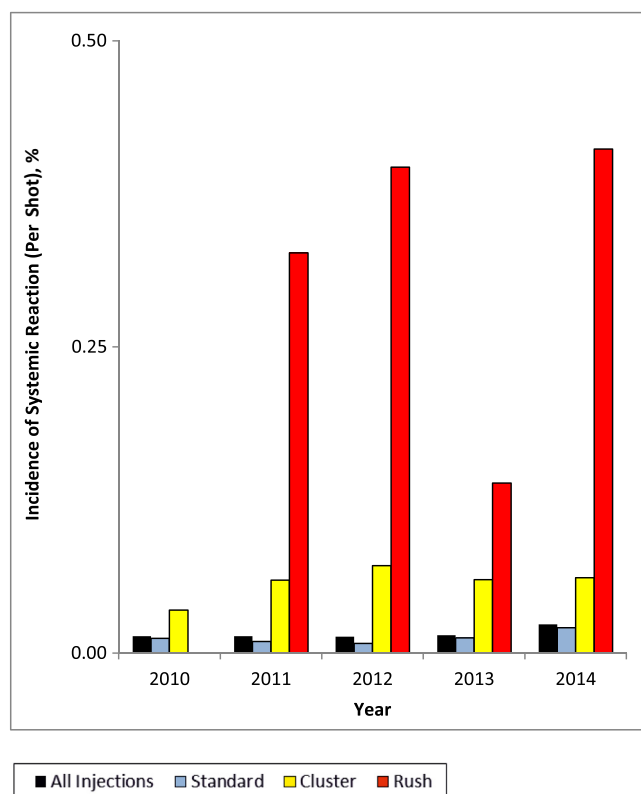


Figure 4. Annual incidence per-shot during a 5-year period (2010–2014) of systemic reactions for standard, cluster, and rush immunotherapy.

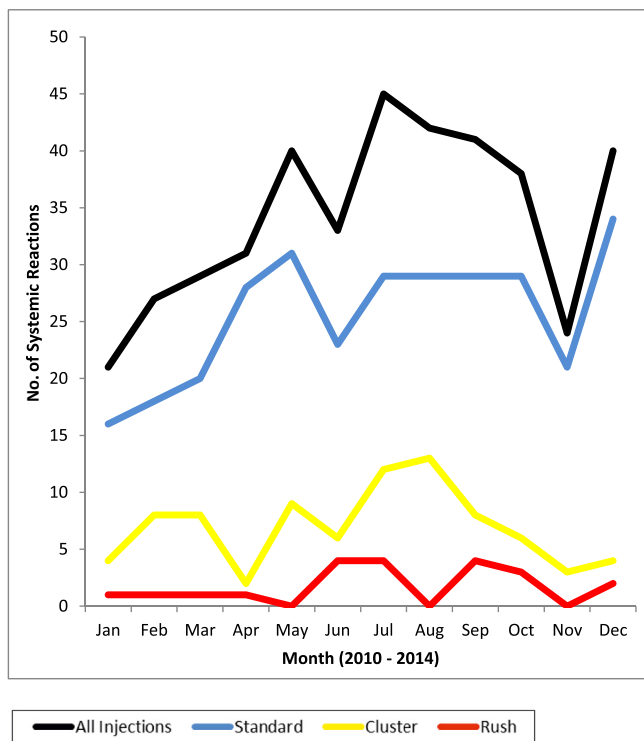


Figure 5. Incidence of systemic reactions by month during a 5-year period (2010–2014) of systemic reactions during standard, cluster, and rush immunotherapy.

regimens adapted from previously published protocols. An additional explanation is that maintenance immunotherapy dosing attempts to balance both safety and efficacy. Third, although there are methods in place to document SRs based on symptom description over the telephone, authors cannot account for all patients experiencing an SR who are nonadherent with the recommended 30-minute waiting rule. Although this measurement error is likely not unique to our practice, it could feasibly bring a slight underestimation of SR incidence.

Importantly, these findings are limited by the absence of data regarding the injections not associated with a SR. These data, if present, would help delineate the demographic characteristics of patients choosing standard, cluster, or rush build-up methods and allow for the exploration of whether asthma, sex, or season may each be a risk factor for SRs among our population. An additional limitation is the use of estimates for the number of injections in the calculation of SR incidence. The total number of injections includes both build-up and maintenance injections, but the calculation of per-shot incidence includes only build-up injections for rush and cluster immunotherapy. Thus, the denominator for the calculation of rush and cluster incidence is lower than the actual number, resulting in a higher calculated SR rate than the actual rate. Conversely, the denominator for the calculation for standard build per-shot incidence includes both build-up and maintenance injections, resulting in a lower calculated per-shot incidence than the actual rate.

Previously published data have recognized female sex, presence of asthma, lack of premedication, hypersensitivity, and current

pollen season as risk factors for SR during subcutaneous immunotherapy.^{9,10} In a similar fashion, this study supports female sex as a risk factor and suggests that seasonality might also play a role. As the study was not designed to specifically evaluate seasonality as a risk factor, the trend toward more SRs during pollen season might be explained by factors other than pollen exposure (eg, increased patient adherence and thus more total immunotherapy injections given during pollen season).

This study included patients receiving immunotherapy for allergic rhinitis, asthma, atopic dermatitis, and multiple allergic conditions. Patients taking β -blockers or angiotensin-converting enzyme inhibitors were not excluded from receiving immunotherapy or from participating in a rapid-build protocol. In our clinical experience, these medications have not been associated with higher rates of SRs; thus, a conscious decision was made not to exclude these patients. Taking place at a single practice during a defined period of time while using the same extracts and dosing, our design limits confounders and provides a robust update to the incidence of SRs. Through continued exploration for risk factors for SRs, improved recognition of risk factors, and additional revisions of rapid-build protocols, we hope to improve on the safety of an increasingly safe office procedure.

To our knowledge, this is the first study of its kind that compares SRs during standard, cluster, and rush subcutaneous immunotherapy and highlights build schedule as the major variable. Although rapid-build schedules pose a higher risk, we found that with appropriate measures, such as premedication protocols and preinjection screening, this risk can be mitigated. These results can help to promote the more widespread use of cluster-build and rush-build immunotherapy. Future directions for our research could include exploring patient adherence as a function of immunotherapy build-up method.

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