

Safety of rush immunotherapy using a modified schedule: A cumulative experience of 893 patients receiving multiple aeroallergens

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ABSTRACT

Conventional immunotherapy (IT) is effective in treating allergic rhinitis, allergic asthma, and chronic rhinosinusitis. Disadvantages include poor compliance, delayed efficacy, and patient frustration. Rush IT, or rapid desensitization, offers the advantages of rapid response, improved compliance, and cost-effectiveness. Although premedication with corticosteroids and antihistamines dramatically reduces systemic reactions, safety remains a primary concern. Two separate half-day schedules with minor differences were used to rapidly desensitize 893 patients (aged 1.5–77 years) in two typical outpatient settings equipped to treat anaphylaxis. All patients exhibited positive skin-prick tests to perennial and seasonal allergens. Diagnoses included allergic rhinitis (857/96%), allergic asthma (505/57%), and chronic rhinosinusitis (384/43%). Five hundred sixty-eight patients were premedicated with prednisone and H1-antihistamine for 3 days. Three hundred twenty-five patients were premedicated for 3 days with prednisone and H1- and H2-blockade. The protocol's final dose ranged from 0.1 to 0.5 mL of a 1:1000 dilution of extracts manufactured by ALK and Greer Laboratories. Patients continued on to higher doses by resuming a conventional schedule. Eighteen patients (2.0%) experienced a mild systemic reaction. All responded to subcutaneous epinephrine and/or nebulized albuterol and were sent home after observation. One patient (0.1%) experienced true anaphylaxis and received appropriate treatment and observation. Our experience with rush IT confirms that maintenance IT can be reached quickly and safely under careful supervision. Caution must be exercised when using this procedure because anaphylaxis does occur. Systemic reactions occur less frequently using a lower targeted final dose than previously described in the literature.

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Key words: Allergen immunotherapy, allergen vaccination, allergic asthma, allergy, asthma, efficacy, rush immunotherapy, rapid desensitization

Therapeutic vaccines containing allergen extracts, otherwise known as immunotherapy (IT), are efficacious in the treatment of allergic rhinitis,^{1–4} allergic asthma,^{5–11} and hymenoptera allergy.^{12,13} Conventional allergen vaccination (CAV) uses a protocol of weekly, gradually increasing dosages of allergen extract until a maintenance dose is reached. Subsequently, the maintenance dose administration is reduced to biweekly or monthly for a 3- to 5-year duration. It is the goal that on completion of the therapy, immunity is induced and remission of the disease is achieved. Effectiveness of the CAV at altering the

immune system is supported by measurable levels of IgG4.¹ CAV's mechanism of action occurs *via* a decrease of T-helper-type-2 cells and an increase of T-helper-type-1 cells that leads to decreased expression of allergic disease.¹⁴

CAV has demonstrated effectiveness in the treatment of a number of allergic conditions; however, its effectiveness is largely limited because of patient adherence. Low adherence rate is the most imposing barrier to the effectiveness of CAV, because the therapy requires long-term commitment and discipline. Adherence rates at 1 year for CAV above 50% are very unusual.^{15,16}

Rapid allergen vaccination (RAV), otherwise known as rapid desensitization or rush IT, may improve adherence by providing the patient with quicker efficacy than CAV schedules and thus reducing morbidity from the allergic disease. Moreover, RAV can eliminate up to 6 months of weekly and costly build-up injections, resulting in cost savings for both the physician and the patient (in terms of time and material).

An immunizing dosage is achieved much more quickly with RAV than with CAV. Through a series of

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Table 1 Demographic data

Demographic	Finding
Total no. of patients	893
Age mean (yr; range)	38 (1.5–77)
Sex, no. (%) of patients	
Male	386 (43.2%)
Female	507 (56.8%)
Diagnoses, no. (%) of patients	
Allergic rhinitis	857 (96%)
Chronic sinusitis	384 (43.0%)
Asthma	505 (56.6%)

increasing doses of allergen extract, a patient may reach an effective “maintenance dose” in a period of 1–7 days.^{10,17,18} The major controversy surrounding this procedure is its safety; more specifically, its potentially increased risk of systemic reactions resulting in anaphylaxis or death.^{19,20} Subcutaneous allergoid preparation can provoke minor systemic reactions with respect to aqueous or depot vaccines. Systemic reactions have been reported to be >15% in previous studies.^{18,21–25} Recently, Sharkey and Portnoy²⁶ reported a systemic reaction rate of 23%. Their report described these reaction rates as comparable with CAV,²⁶ with reported rates varying from 0.8 to 46.7%. Such high rates of reaction are unacceptable for utilization of the procedure in the office setting, and most practicing allergists would agree that these rates are much higher than those occurring in their offices.

Encouraged by the preliminary findings of Inglefield in a 1996 abstract at the annual meeting of the American College of Allergy, Asthma, and Immunology, an effort was initiated to improve this procedure to assure optimal safety. Subsequent research indicated that with careful patient selection, premedication, and a lower targeted end point dose, RAV could be performed safely and effectively in the private clinical setting.²⁷ The purpose of this study was to review the safety of the RAV procedure in the office-based setting of the practicing allergist. This study retrospectively looks at the systemic reaction rate of 893 patients aged 1.5–77 years who underwent the modified rush IT protocol.

MATERIALS AND METHODS

Selection of Patients

The demographics and age distribution of the RAV patients can be found in Table 1. There were 893 patients whose charts were retrospectively reviewed. The age of the patients ranged from 1.5 to 77 years. All were selected from an office-based allergy setting. All patients were diagnosed with one or more of the following conditions: allergic rhinitis, allergic asthma, and

chronic sinusitis; each exhibited IgE positivity by skin-prick testing and exhibited a history consistent with allergic-mediated disease. All patients were given the choice between CAV and RAV. Informed consent, outlining the potentially greater risks for the RAV procedure, including the potentially greater risk of anaphylaxis, was obtained from all patients who underwent the procedure.

Exclusion criteria included the following:

1. A history of anaphylaxis.
2. A forced expiratory volume in 1 second of <70% predicted by pulmonary function testing.
3. A history of cardiovascular disease.
4. Current β -blocker therapy.

The protocol was reviewed and approved by Parkview Institutional Review Board, Fort Wayne, IN.

Percutaneous Allergy Testing

Commercial allergy testing extracts used included 1:10 (w/v) standardized glycerinated extracts from Greer Laboratories (Lenoir, NC). Skin-prick technique was performed with the DermaPick (Greer Laboratories, Lenoir, NC) and ALK-Abello (Hoersholm, Denmark). Intradermal tests were placed with the same allergen extract using a 1:2000 dilution with 25G syringes. Tests were read 20 minutes after placement. Skin reaction was measured as the diameter of wheal and flare in millimeters. Those who tested negative to skin-prick testing underwent further intradermal testing to confirm skin reaction. Intradermal tests were considered positive when the diameter of either the wheal or the flare was at least 5 mm and larger than the negative diluent control.

Allergen Vaccination Extract

Therapeutic vaccines containing allergen extracts were prepared using stock formulations from ALK and Greer Laboratories. Both aqueous and glycerinated extracts were used to achieve a concentrate of ~1:100 w/v of the mixed extract. A combination of 2 to 32 allergens was mixed to achieve a final dilution of 1:100. Serial 10-fold dilutions of this concentrate were prepared identically to that used for CAV. The targeted final dose during the RAV procedure was that of a 1:1000 dilution to minimize systemic reactions. Separate vials were used for pollen and mold extract to reduce proteolytic degradation. All extracts were stored at ~4°C. Therapeutic vaccine varied with each individual patient and was prepared for each patient based on specific allergens identified during testing. Most patients' vaccines included a variety of aeroallergens including a combination of mold, trees, grass, weed, mites, cats, and dogs. Standardized extracts for ragweed, cats, dust mites, and grass were used. The

Table 2 Final dosage concentrations of grass, dust mites, cats, and ragweed extracts

Allergens	Concentration
Grass	4000 BAU in 0.4 cc of 1:10
Dust mites	200 BAU in 0.4 cc of 1:10
Cats	400 BAU in 0.4 cc of 1:10
Ragweed	4.76 U/mL in 0.4 cc of 1:10

BAU = bioequivalent allergy unit.

final dosage concentrations for those allergen extracts are listed in Table 2.

Procedure for RAV

All patients presenting to the clinic who were thought to benefit from IT were given the option to begin this therapy. Patients who were considered acceptable candidates for this procedure as outlined previously were given the option to participate in the RAV procedure as an alternative to CAV. Once candidates were identified, the procedure was scheduled 1–2 weeks later. A 3-day premedication regimen of prednisone and antihistamine was prescribed as follows: for patients aged 1–12 years, prednisone or prednisolone, 20 mg b.i.d.; for ages ≥ 12 years, prednisone, 30 mg b.i.d. The antihistamine included one of the following: cetirizine, fexofenadine, or loratadine at the age-appropriate dosage. Previous side effects, insurance, age, and form (e.g., syrup, pill, chewable, etc.) were all factors considered in choosing the appropriate antihistamine for individual patients. It was not investigated whether the specific antihistamine had an effect on likelihood of systemic reaction. Generally, the antihistamine that the patient had success with previously or was currently using was chosen for the purpose of premedication. An informed consent was explained by a registered nurse and then obtained, with a written consent form signed by the patient, if >18 years of age, or the parent, if the patient was <18 years of age. On the day of the procedure, patients were reassessed with a history, physical examination, and spirometry. Any documented clinical worsening (e.g., upper respiratory infection or significantly decreased spirometry) resulted in rescheduling of the procedure.

The dosing schedule is outlined in Table 3. The administration schedule was developed by reviewing the literature and assessing the reasons other researchers, especially Portnoy *et al.*, experienced relatively high reaction rates.^{23–26} Given the high systemic reaction rate occurring while using the most concentrated vials, the resulting schedule appeared to best minimize reaction risk. The premedication schedule resembles that of previous studies cited in the bibliography.^{28,29} If patients received two injections (e.g., separated pollen

Table 3 Dosing schedule for patients receiving 2–3 hr RAV procedure

	Volume (mL)	Dilution
RAV Procedure Dosing, Time (min)		
0	0.025	1:1,000,000
15	0.25	1:1,000,000
30	0.025	1:100,000
45	0.25	1:100,000
60	0.025	1:10,000
75	0.25	1:10,000
90	0.025	1:1000
105	0.1	1:1000
Post-RAV Procedure Build-Up, Interval		
After 4–10 days	0.1	1:1000
After 4–10 days	0.15	1:1000
After 4–10 days	0.2	1:1000
After 4–10 days	0.3	1:1000
After 4–10 days	0.4	1:1000
After 4–10 days	0.025	1:100
After 4–10 days	0.05	1:100
After 4–10 days	0.1	1:100
After 4–10 days	0.15	1:100
After 4–10 days	0.2	1:100
After 4–10 days	0.3	1:100
After 4–10 days	0.4 (maintenance)	1:100

and fungal allergens), one was administered in each arm using the same schedule. We did not alternate arms for injections. Patients were observed for 30 minutes after their last injection and discharged if stable. After the RAV procedure, patients resumed a CAV schedule until the final desired maintenance dosage was achieved.

COLLECTION OF DATA

The purpose of this study was to investigate, through a retrospective chart analysis, whether the procedure of RAV is safe in the office-based setting of the practicing allergist. The study investigated a group of patients ranging in age from 1.5 to 77 years having undergone the RAV at least 1 year before the study at The Allergy and Asthma Center P.C. (Fort Wayne, IN) and Hickory Allergy & Asthma Center (Hickory, NC). Thus, the patients included in this study have undergone the RAV procedure between the years of 1998 and 2002.

A database was developed for the purpose of organizing the data pertaining to all patients who have undergone the RAV procedure. Variables that were considered and recorded for the purpose of the study include:

1. Age.
2. History and prior diagnoses of rhinitis, sinusitis, and asthma.
3. Local reactions, systemic reactions, anaphylaxis.

The variables of age, rhinitis, sinusitis, and asthma were selected for analysis to provide an idea of the respiratory condition of the patients in this age group that have undergone RAV, as well as give indication of the application and extension of these results to similar cohorts. The variables of local reactions, systemic reactions, and anaphylaxis resulting during the RAV procedure were chosen as indicators of the safety of the RAV procedure.

The results of this study are reported as ratios and standard percentages of the entire cohort. Systemic and local reaction rates and anaphylaxis rates for the patients undergoing RAV in this study are then compared with the reaction rates of CAV published in the literature. Subsequently, these results provide the grounds for the drawing of appropriate conclusions for the study.

RESULTS

A total of 893 patients underwent rapid desensitization using a 2.5-hour protocol (see Table 1).

Systemic Reactions to RAV

Systemic reactions occurred in 18 of the 893 patients (2.0%) between the second and final dose of the procedure and one (0.1%) of the patients experienced anaphylactic shock. A detailed description of each systemic reaction can be found in Table 4. Fourteen of the 18 patients (77.8%) who suffered a systemic reaction were patients with asthma on inhaled corticosteroids, 6 of the 18 patients were men (33.3%) and 12 of the 18 patients were women (66.6%). Statistically, there were no observable differences in reactions in relation to the patients' race, allergies, or the extract used when compared with patients who had no reaction.

All of the patients were treated and sent home the same day. A trained physician or nurse monitored each patient very closely for at least 60 minutes after an adverse event. All of the patients continued with a conventional allergen IT regimen following the rapid protocol. Every systemic reaction occurred between 10 and 15 minutes of the injection; none were immediate. Treatment usually included one or a combination of the following: nebulized breathing treatment with levalbuterol, 0.63 mg, 2 sprays in each nostril of azelastine, and diphenhydramine taken orally or intramuscularly. Every patient that was treated was discharged within several hours, with the exception of one patient who required treatment with subcutaneous epinephrine and hospitalization. Examining the extract composition of those patients experiencing a systemic reaction revealed that all of them had extract containing mold and a high majority contained tree (94.4%), weed (94.4%), and grass (94.4%). The composition of the extract for the patient who experienced anaphylaxis

included mold, tree, weed, grass, and dust mites. See Table 5 for the extract composition of all patients experiencing systemic reactions. The strengths of the vaccine extracts for grass pollen, ragweed pollen, dust mites, and cat dander when systemic reactions occurred are provided in Table 6.

Build-Up Period

After the RAV procedure, patients typically required at least 2 more months of build-up to achieve their targeted maintenance dose (*i.e.*, weekly IT).

DISCUSSION

Therapeutic vaccines containing allergen extracts (IT) are an effective and safe procedure that has been shown to significantly improve symptoms associated with allergic disease.¹⁻¹³ CAV often is viewed by patients and referring physicians as an inconvenient procedure^{15,16} that can take as much as 6 months or longer to reach efficacy. As a result, a strategy that reduces inconvenience and retains the safety associated with CAV would be a welcome treatment option. RAV (rush IT or rapid desensitization) is an alternative procedure that shows great promise to improve convenience and thus improve adherence and efficacy over CAV.

In a previous study of all ages, we investigated the safety and efficacy of RAV in 137 patients. It was found that the systemic reaction rates for RAV compared favorably with the reaction rates of CAV as well as the reaction rates of earlier RAV studies.²⁷ Moreover, those patients who underwent RAV exhibited greater adherence when compared with reported CAV rates.^{27,30}

In previous studies, high rates of systemic reactions have limited the use of RAV by practitioners.^{18,20,22-24} In this study, we found that RAV is just as safe in patients of varying ages from 1.5 to 77 years. Systemic reaction rates for this study compared favorably with those of Portnoy *et al.* and others.²³⁻²⁸ We agree with others that through careful patient selection, routine premedication, and a lower targeted end point dosage, the risk of systemic reactions is greatly reduced.^{26,27,29,31} As with CAV patients, exclusion criteria included the following:

1. A history of anaphylaxis.
2. A forced expiratory volume in 1 second of <70% predicted by pulmonary function testing.
3. A history of cardiovascular disease.
4. Current β -blocker therapy.

The main reason for the reduced systemic reactions compared with previous reports relates primarily to our lower targeted end point vaccination dosage for the RAV procedure. In previous studies, the higher administered dosages led to a high rate of systemic reactions.^{26,27} Clearly, systemic reactions mostly oc-

Table 4 Systemic reaction descriptions

Patient No.	Reaction Type	Dosage	Symptoms	Treatment	Continued CAV
38195	Systemic	0.025 mL of 1:100	Cough, chest tightness, mouth numbness, throat feels "thick"	Nebulized bronchodilator (levalbuterol, 0.63 mg), azelastine, 0.1sp; epinephrine	Yes
31845	Systemic	0.1 mL of 1:100	Chest pressure, swelling in cheeks and tongue, urticaria	Self-limited	Yes
37581	Systemic	0.025 mL of 1:1000	Cough, itchy throat	Nebulized bronchodilator (levalbuterol) 0.63 mg, azelastine	Yes
38471	Systemic	0.025 mL of 1:100	Chest tightness	Nebulized bronchodilator (levalbuterol, 0.63 mg), azelastine	Yes
34619	Systemic	0.025 mL of 1:100	Chest tightness & phlegm	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
32153	Systemic	0.025 mL of 1:1000	Chest tightness	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
31110	Systemic	0.25 mL of 1:1000	Difficulty breathing	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
28060	Systemic	0.025 mL of 1:1000	Tongue itching	Azelastine	Yes
23481	Systemic	0.25 mL of 1:1,000,000	Chest tightness and hoarseness	Nebulized bronchodilator (levalbuterol, 0.63 mg), azelastine	Yes
26652	Systemic	0.1 mL of 1:100	Chest tightness	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
29726	Systemic	0.1 mL of 1:100	Chest tightness	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
31651	Systemic	0.1 mL of 1:100	Throat tightness, short of breath,	25 mg p.o. Benadryl	Yes
25472	Systemic	0.025 mL of 1:100,000	Chest tightness, short of breath	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
31789	Systemic	0.025 mL of 1:10,000	Mild frontal headache, itchy throat	Nebulized bronchodilator (levalbuterol, 0.63 mg), azelastine	Yes
20626	Systemic	0.25 mL of 1:1000	Throat tight	Self-limited	Yes
26293	Systemic	0.1 mL of 1:100	Chest tightness	Nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
20389	Systemic	0.25 mL of 1:1,000,000	Chest and throat tightness, short of breath, cough	Pirbuterol, azelastine, nebulized bronchodilator (levalbuterol, 0.63 mg)	Yes
27691	Anaphylaxis	0.25 mL of 1:100	Anaphylactic reaction	Nebulized bronchodilator (levalbuterol 0.63 mg), epinephrine, lorazepam, azelastine, i.v. Fluids, i.v. Solumedrol	Yes

Table 5 Composition of vaccines used for patients with systemic reactions

Patient No.	Reaction Type	Trees, Grass, and Weeds*	Molds and Inhalants#	Cats	Dogs	Feathers	Corn Pollen
38195	Systemic	X	X	X	X		
31845	Systemic	X	X	X			
37581	Systemic	X	X	X		X	
38471	Systemic	X	X	X	X		
34619	Systemic	X	X		X	X	
32153	Systemic	X	X	X			
31110	Systemic	X	X		X		
28060	Systemic	X	X	X	X	X	
23481	Systemic	X	X	X	X		
26652	Systemic	X	X				
29726	Systemic	X	X	X	X		
31651	Systemic	X	X		X		
25472	Systemic	X	X	X			
31789	Systemic	X	X	X			
20626	Systemic	X	X	X			
26293	Systemic	X	X				
20389	Systemic		X				X
27691	Anaphylaxis	X	X				

*Included the most common tree, grass and weed pollens for area in which patient lives.

#Included common indoor and outdoor molds for area in which patient lives and dust, dust mites, and roaches.

Table 6 Strength of vaccine at time of systemic reactions

Patient No.	Reaction Type	BAUs and Grass	Ragweed (U)	Dust Mites (BAUs)	Cats (BAUs)
38195	Systemic	25	0.02975	1.25	2.5
31845	Systemic	100	0.119	5	10
37581	Systemic	2.5	0.002975	0.125	0.25
38471	Systemic	25	0.02975	1.25	2.5
34619	Systemic	25	0.02975	1.25	
32153	Systemic	2.5	0.002975	0.125	0.25
31110	Systemic	22.5	0.026775	1.125	
28060	Systemic	2.5	0.002975	0.125	0.25
23481	Systemic	0.025	0.00002975	0.00125	0.0025
26652	Systemic	100	0.119	5	
29726	Systemic	100	0.119	5	10
31651	Systemic	100	0.119	5	
25472	Systemic	0.025	0.00002975	0.000125	0.0025
31789	Systemic	0.25	0.0002975	0.00125	0.025
20626	Systemic	22.5	0.026775	1.125	2.25
26293	Systemic	100	0.119	5	
20389	Systemic			0.00125	
27691	Anaphylaxis	250	0.26775	12.5	

BAU = bioequivalent allergy unit.

curred with the final dosage. By reducing this dosage, a significant drop in systemic reactions was observed. Our targeted end point dosage represents a 10-fold reduction in dosage compared with that of Portnoy *et al.*^{27,28}

With the rising costs in the last 10 years for the treatment of asthma and allergic diseases, the cost-effectiveness of treatments has become a major concern for patients and insurance companies alike.³² The latest

immune therapy, Omalizumab, can exceed \$20,000 annually. Because of the rising cost of allergy and asthma treatments, cost-effective health care for allergic patients has become a priority for allergists. Patients who undergo RAV can save up to 6 months of a build-up period, reducing the cost of therapy by as much as 50% in the 1st year of IT (calculated by eliminating 24 weekly vaccinations). The simplification of treatment and reduction of personal economic cost appears to have increased patient adherence as well.²⁸

Inconvenience is cited in previous studies as being the number one reason for patients discontinuing allergen vaccinations.^{12,16,32} Thus, the rate of allergen vaccination dropout is high. In contrast to CAV, RAV has reduced the time period for allergen vaccination by several months, achieved effective doses within weeks, and, as a result, has substantially increased efficacy and adherence to therapy. Other possible advantages of RAV include quicker accruing of IT benefits than with CAV, resulting in less morbidity, decreased medication, decreased symptoms, decreased emergency room visits, and fewer hospitalizations.

The purpose of this study was to investigate, through a retrospective chart analysis of patients on IT, whether the procedure of RAV using a modified 2.5-hour protocol is safe in the office-based setting of the practicing allergist. RAV can be used for the treatment of IgE-mediated diseases that are typically seen in an allergist's office. By performing this in our offices with proper monitoring, medical equipment, and trained personnel, the procedure was accomplished in a safe and controlled environment.

CONCLUSION

RAV using a modified 2.5-hour protocol with pre-medication is a safe and effective procedure for allergic rhinitis and allergic asthma. Patients undergoing this procedure are able to reach a maintenance dosage in a shorter time than with CAV. Caution and clinical judgment should be exercised when using this procedure. It is emphasized that allergists must use their best judgment and experience to select patients for this procedure, just as they would in the careful selection of patients for traditional IT, because anaphylaxis can occur. We found that systemic reactions occur less frequently with this procedure when using lower targeted end point vaccination doses than previously reported, and patients may continue on CAV schedules to achieve the ultimate targeted maintenance vaccine dosage.

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