
Safety of rush immunotherapy to multiple aeroallergens in an adult population

Shelly M. Harvey, MD*; Scot Laurie, MD†; Kathi Hilton, RN‡; and David A. Khan, MD‡

Background: Rush immunotherapy has many potential benefits but a higher incidence of systemic reactions compared with traditional immunotherapy. The safety of rush immunotherapy to multiple aeroallergens has not been widely studied.

Objective: To examine the safety of rush immunotherapy to multiple aeroallergens in a primarily adult population and to identify risk factors for systemic reactions.

Methods: A retrospective review of 65 patients who received rush immunotherapy to multiple aeroallergens in a university-based allergy practice was conducted. All patients were premedicated with prednisone, cetirizine, ranitidine, and zafirlukast or montelukast. Percutaneous skin testing was performed, major allergen content was analyzed in every fourth patient's immunotherapy extract, and systemic reactions were graded.

Results: Systemic reactions were observed in 25 patients (38%). All systemic reactions occurred with the final 3 doses of the protocol. Most (72%) occurred after the final dose of the protocol. Nineteen (76%) of the reactions were mild, 5 (20%) were moderate, and 1 (4%) was severe. Systemic reactions were associated with a higher degree of skin test sensitivity and the presence of weed or dog allergen in the extract (vaccine).

Conclusions: Rush immunotherapy is associated with a relatively high incidence of systemic reactions, but most reactions are mild and easily treated. The degree of skin sensitivity to the allergens administered and the presence of dog or weed allergen in the extract may be predictors for the development of systemic reactions.

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INTRODUCTION

Immunotherapy has been proven effective as treatment for allergic rhinitis,^{1–3} allergic asthma,^{4–6} and Hymenoptera sensitivity.^{7,8} Conventional immunotherapy generally consists of weekly or biweekly allergen injections, administered in slowly increasing doses until maintenance doses are reached at approximately 4 to 6 months. Rush immunotherapy (RIT) is a technique of advancing an allergic patient to a maintenance dose of an extract over a shorter time frame than that required with traditional immunotherapy. RIT was first described by Freeman⁹ in 1930 for the treatment of allergen-sensitive asthma, hay fever, and 1 case of fish allergy. This method of rapid desensitization has been performed primarily for drug^{10,11} and venom allergy.^{12,13} The safety and efficacy of RIT have not been widely studied for aeroallergen immunotherapy, especially with multiple aeroallergens in adults.

Traditional immunotherapy, although effective, presents the patient with certain obstacles that must be overcome to achieve clinical benefit. The traditional build-up injection schedule requires a significant time commitment and a high

level of compliance. Other potential disadvantages of traditional immunotherapy are the delay in efficacy, the cost, and the time expenditure of frequent weekly injections.

Ideally, immunotherapy should provide the allergic patient with maximal clinical benefit and minimal risk. The primary concern with RIT, compared with traditional immunotherapy, has been the higher rate of systemic reactions. Systemic reaction rates with RIT have ranged from 7.2% to 73% in previous studies.^{14–21} In contrast, the systemic reaction rate with conventional immunotherapy is 0.1% to 0.51% per injection or 7% to 12.5% per patient.^{22–25} Premedication with corticosteroids and antihistamines has been shown to lower the incidence of systemic reactions with RIT significantly.^{15,19} Since cysteinyl leukotrienes are released during anaphylaxis,²⁶ it is possible that the use of leukotriene receptor antagonists may attenuate a reaction.

Since most patients receiving aeroallergen immunotherapy are receiving multiple, not single, allergens, the safety of RIT using multiple allergens is an important question. Furthermore, in clinical practice, standardized and nonstandardized allergen extracts (vaccines) are used together. Portnoy et al^{14–16} have reported on the safety of multiple allergen RIT in studies of 11 to 22 children. In adults, only a single RIT study using only standardized pollen extracts exists.¹⁹ The purposes of this report are to evaluate the safety of RIT with multiple aeroallergens in a primarily adult population and to determine if certain patient variables can be used to predict which patients are more susceptible to adverse reactions. To our knowledge, this is the first report on the safety of multiple aeroallergen RIT using standardized and nonstandardized extracts in adults.

* Pediatric Allergy/Immunology Associates, P.A., Dallas, Texas.

† Dallas Allergy and Asthma Center, Dallas, Texas.

‡ Division of Allergy & Immunology, University of Texas Southwestern Medical Center, Dallas, Texas.

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METHODS

Patients

From January 1997 to July 2002, 65 patients received RIT in a single-physician, university-based allergy clinic. Only patients with positive prick skin test results to aeroallergens received immunotherapy. Any patient deemed appropriate for inhalant immunotherapy was offered RIT as an alternative, and approximately 80% of patients selected RIT. Patients were informed of the potential for higher systemic reactions based on previous published reports and signed informed consent documents.

Allergy Skin Testing

Percutaneous skin testing was performed using glycerinated allergen extracts (Hollister-Stier, Spokane, WA), applied with a bifurcated needle. The skin test panel consisted of 38 aeroallergens, including 5 grasses, 11 trees, 9 weeds, 8 molds, 2 dust mites, and 1 each of dog, cat, and cockroach. Histamine (184 mg/mL) was used as a positive control, and isotonic sodium chloride solution was used as a negative control. Wheals were measured after 15 minutes, and the mean cross-sectional diameter in millimeters was used for grading from 0 to 4+ as follows: 1 to 3 mm, 1+; 4 to 5 mm, 2+; 6 to 10 mm, 3+; and more than 10 mm, 4+. In general, 3+ and 4+ reactions were considered positive, and 2+ reactions were positive if they correlated with the clinical history.

To evaluate the relationship between skin test reactivity and adverse reactions to RIT, 2 separate scoring systems were formulated. First, a cumulative skin test score was determined for each patient by adding the skin test responses (0 to 4+) to each of the 38 aeroallergens tested. Using the same method, each patient was also given a second cumulative extract score, representing their skin test reactivity to only the allergens that were included in their RIT extract.

Allergen Extracts (Vaccines)

All immunotherapy extracts (vaccines) were commercially prepared by Hollister-Stier, premixed in equal parts without added diluent. Most were glycerinated. Usually, no more than 10 allergens were included in a single extract. Molds were generally separated from pollens, but occasionally when patients were receiving less than 10 total allergens, molds and pollens were combined in a single extract.

Major allergen content was analyzed in every fourth patient's extract (vaccine). In this subset of patients, the major allergens for dust mite, Der p 1 and Der f 1, were administered at a mean of 800 allergy units (AU) per dose (recommended dosing is 600 AU per dose for Der p 1 and 2,000 AU per dose for Der f 1²⁷). The standardized acetone precipitated cat pelt Fel d 1 mean dose was 837 bioequivalent allergen units (BAU) per dose (recommended dosing is 2,000 to 3,000 BAU per dose²⁷). Orchard and timothy grasses were dosed on average at 6,168 and 5,824 BAU per dose of Dac g 5 and Phl p 5, respectively (recommended dosing is 4,000 BAU per dose²⁷). The giant, short, western ragweed mix provided a mean of 3.7 antigen E units per dose (recommended dosing is

6 to 24 antigen E units per dose²⁷). Although the amount of short ragweed allergen (antigen E units) administered appears suboptimal, it is known that there is significant cross-reactivity among giant, short, and western ragweed in the mix used at our institution.²⁸

RIT Protocol

All patients were premedicated the day before RIT and the morning of RIT with the following: prednisone, 40 mg once daily; cetirizine, 10 mg once daily; ranitidine, 150 mg twice daily; and zafirlukast, 20 mg twice daily, or montelukast, 10 mg once daily. Vital signs were obtained at the beginning of the protocol, before each injection, and hourly thereafter. A nurse and physician were immediately present during the entire protocol. Baseline spirometry was performed in asthmatic patients. All patients signed an informed consent.

The protocol for RIT (Table 1) was developed using the 1-day RIT protocol by Sharkey and Portnoy,¹⁶ used in children, as an initial framework. Before 2000, our protocol included an eighth dose of 0.1 mL of concentrate. Only 12 of the 65 patients received this protocol. The protocol was changed in 2000 due to more frequent reactions to the 0.1-mL dose. All injections were delivered in the allergy clinic during a 4-hour period. Patients were observed for 2 hours after the last injection.

Grading of Reactions

Wheals at injection sites of more than 20 mm were considered large local reactions. Systemic reactions were categorized as mild if the patient had only subjective complaints, cough without a decrease in forced expiratory volume in 1 second (FEV₁), a limited number of urticarial lesions, or flushing. Reactions of moderate severity included widespread urticaria, angioedema, wheezing with respiratory distress or decrease in FEV₁, or abdominal symptoms. Reactions were considered severe if the patient developed hypotension or severe respiratory distress. We elected not to treat mild reactions with epinephrine but instead observed them carefully for progression. When reactions occurred that required treatment, the RIT protocol was stopped.

Subsequent Injections

For most patients, the final dose received during RIT was repeated for the first post-RIT injection. For patients who experienced a systemic reaction during RIT, this dose was

Table 1. Rush Immunotherapy Protocol

Injection No.	Time, min	Concentration, volume:volume	Volume, mL
1	0	1:10,000	0.3
2	30	1:1,000	0.3
3	60	1:100	0.1
4	90	1:100	0.3
5	120	1:10	0.1
6	180	1:10	0.2
7	240	Undiluted concentrate	0.05

Table 2. Demographic Data

Demographic	Finding
Total no. of patients	65
Age, mean (range), y	36 (13–71)
Sex, no. (%) of patients	
Male	31 (48)
Female	34 (52)
Diagnosis, no. (%) of patients	
Allergic rhinitis	65 (100)
Asthma	24 (37)
Allergen sensitivity, no. (%) of patients	
Grasses	47 (72)
Trees	57 (88)
Weeds	51 (79)
Molds	34 (52)
Dust mites	44 (68)
Cat	35 (54)
Dog	28 (43)
Cockroach	28 (43)

lowered. Following RIT, a typical patient would receive weekly injections with the concentrated extract as follows: 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mL. Injections of 0.5 mL would then be administered once at 2 weeks, then once at 3 weeks, then at monthly intervals.

Statistical Analysis

Exploratory data analysis was performed using SPSS statistical software version 9.0 (SPSS Inc, Chicago, IL). A bivar-

iate correlation was performed using Pearson correlation. Based on cross-tabulation patterns, further testing of significance was performed using χ^2 analysis.

RESULTS

Patient Demographics

Patients ranged in age from 13 to 71 years, with a mean age of 36 years (Table 2). Males and females were almost equally represented. All of the patients had allergic rhinitis, and 37% also had asthma. No patients were taking β -blockers, and none had significant cardiovascular disease. The total number of allergens received by each patient ranged from 1 to 32, and 45% of the patients received 2 separate injections. Only 1 patient received a single allergen, and the average number of allergens per extract (vaccine) was 9. Grasses were present in 72% of the extracts, trees in 88%, weeds in 79%, molds in 43%, dust mite in 68%, cockroach in 19%, cat in 37%, and dog in 23%. Spirometry demonstrated a range in FEV₁ from 71% to 121% predicted.

Systemic Reactions during RIT

Of the 65 patients who received RIT, 25 (38%) had systemic reactions, and 27 (42%) had large local reactions. Nineteen (76%) of the systemic reactions were considered mild, 5 (20%) were moderate, and 1 (4%) was severe (Table 3). No patients had airway compromise, none required hospitalization, and only 1 patient developed hypotension. Treatment of systemic reactions depended on the severity of the reaction. Moderate-to-severe reactions were treated with epinephrine

Table 3. Moderate-to-Severe Systemic Reactions

Patient No.	Reaction	Severity	Eliciting Dose	Treatment	Time to reaction, min
4	Lip swelling, nasal congestion, chest tightness, abdominal cramping, nausea, vomiting	Moderate	0.2 mL 1:10	Hydroxyzine, 75 mg; levocabastine, 2 gtts OU; epinephrine, 0.3 mg s.c.; loratidine, 10 mg; albuterol, 2 puffs	20
6	Facial and trunk flushing, abdominal cramping, palmar pruritus	Moderate	0.05 mL concentrate	Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg	30
9	Nasal congestion, sneezing, axillary pruritus and erythema, decreased FEV ₁	Moderate	0.1 mL concentrate	Albuterol, 5 puffs; albuterol nebulizer, 0.5 mL; ipratropium, 4 puffs; prednisone, 40 mg; cetirizine, 10 mg	35
22	Severe abdominal cramping	Moderate	0.2 mL 1:10	Epinephrine, 0.3 mg s.c.; rofecoxib, 50 mg	45
31	Cough, wheezing, chest tightness, facial flushing, palmar pruritus	Moderate	0.05 mL concentrate	Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg; albuterol, 2 puffs	40
65	Hypotension (systolic blood pressure 50 mm Hg), urticaria, pruritus, facial angioedema	Severe	0.1 mL 1:10	Epinephrine, 0.5 mg intramuscularly 2 times; intravenous fluids, 1 L; cetirizine, 10 mg; prednisone, 40 mg; ranitidine, 150 mg	55 (mild), 150 (severe)

Abbreviations: FEV₁, forced expiratory volume in 1 second; gtts OU, drops in both eyes; s.c., subcutaneous.

Table 4. Variables Correlating with Systemic Reactions during Rush Immunotherapy

Variables	Pearson correlation	P value
Allergen in extract		
Grass	0.065	.30
Tree	0.104	.21
Weed	0.260	.02*
Mold	−0.241	.03*
Dust mite	0.005	.48
Dog	0.242	.03*
Cat	0.116	.18
Cockroach	−0.132	.15
Skin test score		
Cumulative skin test score	0.078	.27
Cumulative extract score	0.207	.049*
Diagnosis of asthma	0.116	.18

* Statistically significant.

in all but 1 patient, who had isolated bronchospasm with a decrease in FEV₁ and was treated with inhaled bronchodilators alone. A single patient who had persistent flushing and palmar pruritus despite treatment with cetirizine also received epinephrine. Of the 19 patients with mild reactions, 15 received oral antihistamines, 3 received oral prednisone, 2 received albuterol, and 1 received ocular antihistamine. Four patients with mild reactions received no treatment. All of the patients with mild reactions had improvement in their symptoms before discharge. Only 1 patient had progressions of symptoms despite initial therapy. The frequency of symptoms in the 25 patients with systemic reactions were as follows in order of frequency: flushing, 56%; pruritus, 40%; rhinitis, 32%; cough and chest tightness, 28%; wheezing and decreased FEV₁, 12%; urticaria and angioedema, 12%; gastrointestinal and uterine symptoms, 12%; and hypotension, 4%. Moderate-to-severe systemic reactions are described in more detail in Table 3.

Of the 25 systemic reactions, 18 (72%) occurred after the last dose of the protocol. Another 4 (16%) occurred after the second-to-last dose. The remaining 3 (12%) occurred after the third-to-last dose. Two patients did well during RIT but developed delayed urticarial reactions 7 and 13 hours after completion of the protocol. Most reactions began 20 to 90 minutes after the eliciting dose. The mean time to reaction, excluding the 2 patients with delayed systemic reactions, was 50 minutes.

The only severe reaction occurred in a 29-year-old woman who began developing pruritus on her neck 55 minutes after the third-to-last injection of the protocol. The next injection was held, but she developed urticaria that was treated with cetirizine and prednisone. Ninety minutes after the onset of her symptoms, the patient acutely worsened and became hypotensive. She was treated with 2 doses of epinephrine, 0.5 mg, administered intramuscularly with prompt resolution of her hypotension. Her course after RIT was uneventful, and she reached a maintenance dose of 0.5 mL of concentrate.

Variables Correlating with Systemic Reactions

Systemic reactions during RIT correlated positively with the presence of weed or dog allergen in the extract ($P = .02$ and $.03$, respectively) (Table 4). Interestingly, the presence of mold in the extract (vaccine) had a negative correlation with systemic reactions ($P = .03$). However, this was only true for patients in whom mold was mixed with pollens. The cumulative extract score correlated with systemic reactions ($P = .049$), but the cumulative skin test score did not.

Systemic reactions did not correlate with age, sex, the presence of large local reactions, asthma, or the number of allergens administered to each patient. In addition, the presence of grasses, trees, dust mites, cockroach, or cat was not predictive of systemic reactions. There was also no correlation among systemic reactions, the type of pollen in the extract, and the month or season that the pollen is most prevalent in the environment.

Reactions after RIT

Thirteen (20%) of the patients had systemic reactions after RIT. Of these, 46% occurred with the first post-RIT dose. Four (31%) occurred with the second post-RIT dose, and the remaining 3 reactions occurred with the third, fourth, and fifth post-RIT doses. Ten (77%) of the reactions were considered mild, 2 (15%) were moderate, and 1 (8%) was severe. Reactions consisted predominantly of pruritus, flushing or urticaria, and cough. The patient with the severe systemic reaction had done well during the RIT protocol, then developed hypotension and syncope with the fourth post-RIT dose. This patient was the only patient who discontinued further immunotherapy. The incidence of systemic reactions after RIT correlated with strong skin test reactivity to grasses ($P < .05$). There was no correlation between post-RIT systemic reactions and the incidence of systemic reactions during RIT, the incidence of local reactions, or the type of allergens included in the extracts (data not shown).

DISCUSSION

The systemic reaction rate of 38% observed in this study is comparable to other studies that evaluated the safety of RIT, with systemic reaction rates ranging from 7.2% to 73%.^{14–21} Of the systemic reactions, most (76%) were mild, with symptoms consisting of rhinorrhea, flushing, and pruritus. Most of these patients were given antihistamines with or without corticosteroids, with resolution of their symptoms. The 5 patients with moderate systemic reactions had symptoms of abdominal cramping, nausea and vomiting, or chest tightness and wheezing. Only 1 of these patients had a decrease in FEV₁, which resolved with inhaled bronchodilators. The 1 patient with a severe systemic reaction developed mild symptoms of pruritus 55 minutes after an injection, then acutely worsened 90 minutes later with hypotension. This emphasizes the importance of a long observation period (2 hours in this study) following RIT, especially for patients with systemic reactions, regardless of severity.

The time to reaction after the eliciting dose averaged 50 minutes in this study. This is longer than the usual time to reaction seen with conventional immunotherapy but consistent with findings from other RIT studies that report average time delays of 42 to 60 minutes.¹⁴⁻¹⁶ This relative delay could be a manifestation of premedication, or it could be secondary to some sort of cumulative dosing effect with RIT. Based on this observed time delay to reactions, we recommend an observation period of 90 to 120 minutes after the last dose of RIT. The 2 patients with delayed systemic reactions at 7 and 13 hours had isolated urticarial lesions, which resolved with antihistamines and corticosteroids. It is unclear why these patients' symptoms were so markedly delayed but important to note that the reactions were mild and not life-threatening. Since all of the moderate-to-severe reactions associated with RIT occurred in the office setting, we do not believe it is mandatory for RIT patients to have self-injectable epinephrine available.

The protocol used in this study is fairly aggressive, achieving a relatively high immunotherapy dose (1:10 maintenance dose) within 4 hours. Most (72%) of the systemic reactions occurred after the final dose of the protocol, and another 16% occurred after the second-to-last dose. If the protocol were altered to stop at 0.2 mL of the 1:10 dilution (the second-to-last dose), it is possible that the systemic reaction rate could have been as low as 10.8%. If the protocol ended yet another dose earlier, the systemic reaction rate might have been 4.6%. Based on these data, a less aggressive protocol is recommended, since it would still hasten considerably the build-up phase of immunotherapy and provide improved safety. Nevertheless, it is prudent to mention that the most severe reaction seen here occurred after a relatively low dose, 0.1 mL of a 1:10 dilution.

In deciding which patients are candidates for RIT, it would be useful to predict what type of patient may be at higher risk for the procedure. In this analysis, the diagnosis of asthma did not increase the incidence of systemic reactions. However, these patients were all asymptomatic at the time of the procedure with normal or near-normal spirometry results. The incidence of systemic reactions did not correlate with age, sex, the presence of large local reactions, or the number of allergens administered. The presence of weed or dog allergen correlated positively with systemic reactions. In contrast, the presence of mold in the extract (vaccine) appeared to have a negative correlation with systemic reactions. This negative correlation between mold and systemic reactions did not hold true when the molds were kept separate from the pollens. Explanations for this observed effect are that the mold partially degraded the pollen allergens or had a dilutional effect on the pollens. It has been shown that the proteases in some molds decrease the relative potency of pollen allergens, first observed 30 days after mixing, with maximum decreased potency at 60 days.^{29,30} Most of our patients began the RIT protocol 4 to 5 weeks after the extracts were mixed.

The degree of skin test sensitivity to the allergens in the extract (vaccine) was predictive of systemic reactions during RIT. This correlation has been seen by several other investigators.^{14,15,20} Portnoy et al¹⁵ found the pretreatment wheal size

to be the most important predictor of systemic reactions. Bousquet et al²⁰ stated that "the sensitivity of the patients evaluated by the skin prick test end point was . . . related to the rate of systemic reactions." It can be concluded that, based on skin testing, individuals highly allergic to multiple allergens are at increased risk for systemic reactions to RIT.

During the weekly injections following RIT, 13 patients (20%) developed systemic reactions. Of these, 46% occurred after the first post-RIT dose. The doses eliciting the reactions were equal to the final RIT dose administered in 5 of the 6 patients and lower in 1 patient who had a systemic reaction during RIT. This 20% rate of subsequent systemic reactions is higher than the rate seen by Sharkey and Portnoy¹⁶ in children, where only 1 (4.5%) of 22 had a systemic reaction in 3 months of follow-up. Given that the 2 protocols are different in terms of speed of the protocol, final dose, ultimate maintenance dose, premedication regimen, and age of population treated, it is difficult to make any conclusions by comparison. Whether the incidence of systemic reactions following RIT may be lowered by decreasing the first post-RIT dose or with premedication before the first several post-RIT doses is unclear and requires further study.

There are several potential limitations to this study. Since it was a retrospective study, it is possible that there was an underestimation of systemic reactions due to less rigid documentation of adverse reactions. Although possible, this is unlikely to have occurred, given the careful monitoring and proactive solicitation of even minor symptoms. Most of the allergen extracts (vaccines) used are not available in standardized form, making it difficult to generalize our findings to other patient groups and practices. The premedication regimen used was fairly comprehensive, but it is possible that other medications or dosing schedules would be more protective against systemic reactions.

Patient satisfaction was high in our patient population. No patient expressed regret for choosing RIT over conventional immunotherapy. Even patients with significant systemic reactions were satisfied with RIT and, when directly questioned, would choose it again. In only 1 of 65 patients was immunotherapy discontinued due to a severe systemic reaction that occurred after RIT. The main reasons for the high patient satisfaction included convenience, the ability to achieve higher allergen doses, improved or faster symptomatic relief from allergic rhinitis and/or asthma, and, in some cases, lower cost to the patient. Although a formal cost analysis was not performed, most of our patients who underwent RIT were managed care patients who paid a single copayment for their RIT, as opposed to the multiple copayments they would have incurred with traditional build-up.

Rush immunotherapy with multiple aeroallergens is associated with a higher systemic reaction rate than conventional immunotherapy. In this retrospective review, however, most systemic reactions were manageable with minimal intervention. This 4-hour RIT protocol with premedication is well tolerated in most patients, and even in those experiencing systemic reactions, patient satisfaction is high. Modification of this

current protocol, with a lower final allergen dose (1:10 dilution, 0.1 or 0.2 mL), is recommended, particularly for patients with a high degree of skin test reactivity to allergens in their extracts. Due to the relative delay of reactions, it is clear that the observation period following RIT should be prolonged compared with traditional immunotherapy. Through this and future investigations, RIT may prove to be an attractive alternative to conventional immunotherapy in select patients.

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Requests for reprints should be addressed to:

David A. Khan, MD

University of Texas Southwestern Medical Center

Division of Allergy & Immunology

5323 Harry Hines Blvd

Dallas, TX 75390-8859

E-mail: Dave.Khan@UTSouthwestern.edu