

Safety of multiple aeroallergen rush immunotherapy using a modified schedule

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ABSTRACT

Rush immunotherapy (RIT) accelerates the build-up phase of traditional IT. The biggest potential benefit of using RIT is decreased time to symptomatic improvement. However, aeroallergen RIT carries an increased risk of systemic reaction (SR) compared with traditional IT. This study was designed to assess the safety of a modified 1-day multiple aeroallergen RIT protocol. A retrospective chart review was performed of 138 patients from an outpatient, university-based allergy practice who underwent RIT between November 2007 and February 2011. The RIT protocol consisted of eight injections over 5 hours, and stopped at one 10-fold dilution below the maintenance vial. All patients were premedicated on the same day of RIT with prednisone and histamine 1 and 2 receptor blockers. Primary end point observed was rate of SR. One hundred thirty-eight patients received a total of 2911 RIT injections. Thirty-eight patients (28%) had SRs. The SR rate per injection was 1.3%. Most of the reactions (82%) occurred after the last dose of the protocol. No patients with SR had severe anaphylaxis requiring emergency department support or hospitalization. The post-RIT SR rate was within the range seen with traditional IT. Well-controlled asthmatic patients were not at increased risk of SR compared with nonasthmatic patients. Modification of RIT to end at one 10-fold dilution below the maintenance vial for multiple aeroallergen RIT did not significantly decrease the SR rate compared with other protocols that end at the maintenance vial. Unlike hymenoptera RIT, aeroallergen RIT continues to be associated with a high risk of SR compared with traditional IT.

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Traditional aeroallergen immunotherapy (IT) schedules require patients to build to a target dose gradually over several months. The safety and efficacy of this build-up method has been well established.¹ However, pitfalls include frequency of injections, length of treatment, and delayed time to symptomatic improvement, which cause many patients to discontinue treatment before the recommended 3–5 years.² Patient adherence has been estimated to be as low as <50% in the 1st year, the majority of which consists of the build-up phase.³ Accelerated schedules, such as cluster, rush, and ultrarush, have been developed over the past several decades for both aeroallergens and Hymenoptera venom to resolve some of these pitfalls.

Rush IT (RIT) is a method that “rushes” or accelerates the initial build-up phase of IT with the goal of achieving a therapeutically effective dose faster than traditional build-up schedules. Depending on the protocol, the maintenance dose may be achieved in as early as 1 day, as opposed to 6–8 months with traditional IT.³ Currently, there are no specific recommen-

dations as to the scheduling or dosing of aeroallergen RIT. Initial protocols for individual aeroallergens published in the 1970s and 1980s consisted of 7–10 injections administered over 3–7 days to the maintenance dose.⁴ More recently, RIT protocols have included multiple aeroallergens and condense the build-up phase into 1 day, with the most accelerated schedule involving seven injections over 4 hours to the maintenance vial.^{4,5} Controlled efficacy studies have shown that symptomatic improvement is possible after reaching maintenance doses by RIT schedules.⁶

The major limitation of aeroallergen RIT is an increased risk of systemic reactions (SR). This is in contrast to accelerated Hymenoptera IT schedules, where studies have shown comparable or superior efficacy and safety compared with traditional IT.⁷ The published SR rates with aeroallergen RIT have been widely variable, ranging between 15 and 100% of patients using single-allergen vaccines, and 23–73% using non-cross-reactive multiple aeroallergen mixtures.^{4,6} This is considerably higher than traditional IT, which ranges from 7 to 12.5% per patient (0.1 to 0.51% per injection).^{5,8}

To improve safety outcomes, modified aeroallergen RIT protocols have been developed.^{4,5,9,10} The most common modification has been the use of premedication with oral corticosteroids and histamine 1 and 2 receptor blockers. Others have included leukotriene receptor antagonists, ketotifen, theophylline, and omalizumab.^{11–13} Additionally, RIT protocols have been

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modified to end at lower doses of the maintenance vial or at one 10-fold dilution below the maintenance vial.^{3–5} The remaining build-up to the target maintenance dose then follows a traditional IT schedule.

A third modification involves patient selection. Careful selection of RIT candidates has been shown to improve safety outcomes. In a 1989 study evaluating the safety of RIT in asthmatic patients, Bousquet and colleagues found that baseline forced expiratory volume in the 1st second (FEV₁) was a predictor of anaphylaxis during RIT, and that asthmatic patients with an FEV₁ < 80% were at a significantly increased risk compared with asthmatic patients with an FEV₁ > 80%.¹⁴ Although these modifications have improved the safety outcomes of aeroallergen RIT, the reported SR rates vary widely (3–79% of patients) and remain higher than traditional IT.⁶

We report our experience with a modified multiple aeroallergen RIT protocol using a lower RIT end dose, same-day premedication with prednisone and histamine receptor 1 and 2 blockers, and careful patient selection. This protocol advances the patient to one 10-fold dilution below the maintenance vial over 5 hours. Because others have observed a high incidence of SRs at the first and second post-RIT doses, we repeated the last dose for 3 weeks, with a total of 11 weeks to the maintenance dose.⁵ We hypothesized that these modifications would decrease the rate of SR closer to traditional IT. To our knowledge, this represents the first published protocol using a 1-day schedule with same-day premedication.

METHODS

Patient Population and Data Collection

We conducted a retrospective chart review of patients who underwent RIT to multiple aeroallergens between November 2007 and February 2011 at a university-based, outpatient allergy practice under the approval of the Institutional Review Board at Vanderbilt University. Patients presented with symptomatic rhinitis and were diagnosed with allergic rhinitis based on skin-prick and intradermal testing to multiple aeroallergens. Patients with positive skin testing were considered candidates for RIT. Exclusion criteria included poorly controlled asthma (FEV₁ < 70%), significant cardiovascular disease, β -blocker use, and patients on omalizumab. All patients underwent the same RIT protocol regardless of degree of reactivity on skin testing.

The primary end point was SR occurrence during RIT and the “post-RIT” period, which we defined as the remaining build-up phase and the subsequent maintenance period up to February 2011. Other data collected included SR severity, concurrent outpatient medications, number of injections administered per

patient, peak expiratory flow rate (PEFR), and comorbid conditions. Reactions were diagnosed based on clinical signs and symptoms at the time of the reaction. Reaction severity was determined retrospectively using the World Allergy Organization grading system.¹⁵

Vaccine Preparation

Mixed aeroallergen vaccines were prepared based on the results of individual skin testing and the inherent proteolytic activities of the extracts. Maintenance vials (1:1 v/v) were prepared by 1:10 dilutions of stock extract formulations (Table 1). Subsequent vials were prepared by serial 10-fold dilutions of the maintenance vials.

Premedication

Patients received premedication starting on the morning of RIT. Patients were given prescriptions for prednisone at 60 mg to be taken 2 hours before arriving to the clinic. Cetirizine at 10 mg and famotidine at 40 mg (or ranitidine at 300 mg) were administered in the clinic 30 minutes before the first injection. Vital signs and PEFR were obtained on all patients before and after RIT. In patients with asthma, RIT was canceled if the patient had an FEV₁ of 15% below their baseline on the morning of RIT. RIT was also canceled if the patient was acutely ill or did not take their prednisone as instructed. Patients who were chronically taking other allergy medications, such as montelukast, were continued but not started anew for the purposes of RIT.

RIT Protocol

A total of eight injections (two injections per dilution) were administered over 5 hours (Table 2). The initial dose of the protocol was 0.05 mL 1:10,000 v/v and the final dose was 0.2 mL 1:10 v/v. Injections started 15 minutes apart, and then prolonged to 30 minutes and then 60 minutes as the protocol progressed to higher doses. Patients were observed for 1 hour after administration of the last dose. Post-RIT, the last dose of the protocol was repeated for 3 weeks (Table 3). Thereafter, patients continued on a weekly build-up schedule to the maintenance dose as per our traditional IT schedule, for a total of 11 weeks. Reactions were treated as per the standard of care with epinephrine, histamine receptor blockers, and corticosteroids. RIT was discontinued with development of an SR.

Adherence

To compare adherence between RIT and traditional IT patients, we retrospectively reviewed all patients who started either treatment between January and De-

Table 1 Allergen extracts and maintenance vial concentrations

Allergen Extract	Concentration of Maintenance (1:1 v/v) Vial	Manufacturer
Standardized extracts		
Dust mite		Hollister-Stier
<i>Dermatophagoides farinae</i>	500 AU/mL	
<i>Dermatophagoides pteronyssinus</i>	500 AU/mL	
Cat	1000 BAU/mL	Greer
Grasses		Hollister-Stier
Kentucky bluegrass	1000 BAU/mL	
Orchard	1000 BAU/mL	
Redtop	1000 BAU/mL	
Timothy	1000 BAU/mL	
Sweet vernal	1000 BAU/mL	
Meadow fescue	1000 BAU/mL	
Perennial rye	1000 BAU/mL	
Bermuda	1000 BAU/mL	
Nonstandardized extracts		
Johnson Grass	1:100 w/v	Hollister-Stier
Dog	1:100 w/v	Hollister-Stier
Trees	1:100 w/v	Greer
Eastern sycamore, sweet gum, white mulberry, elm mix (American and Chinese), eastern cottonwood, oak mix (black, red, and white), sugar maple-box elder mix, birch mix (black, red, and white), red cedar, pecan pollen- shagbark hickory mix, ash mix (green and white), acacia, mountain cedar, and olive		
Weeds	1:100 w/v	Greer
Cocklebur, lambs quarter, rough pigweed, giant ragweed, short ragweed, sage mix (prairie sage and common sagebrush), dock- sorrel mix (yellow dock and sheep sorrel), kochia, English plantain, and nettle		
Molds		Greer
<i>Alternaria</i> , <i>Aspergillus</i> , <i>Helminthosporium</i> , <i>Hormodendrum</i> , and <i>Penicillium</i>	1:100 w/v	
<i>Curvularia</i> , <i>Fusarium</i> , <i>Mucor</i> , <i>Pullularia</i> , and <i>Rhizopus</i>		

BAU = bioequivalent allergy units; AU = allergy units.

ember of 2008. Adherence was measured by the number of patients who were still on IT as of February 2011.

Statistical Analysis

Descriptive statistics were expressed as proportions for categorical variables and as means and standard deviation for continuous variables. Mann-Whitney *U* test for continuous variables or Pearson chi-squared test for categorical variables was used to compare between groups. Fisher's exact test was used instead of Pearson chi-squared test when number of subjects were small. R-software Version 2.11.1 was used for

data analyses.¹⁶ A two-sided 5% significance level was used for all statistical inferences.

RESULTS

Patient Demographics and Baseline Characteristics

One hundred thirty-eight patients completed RIT between November 2007 and February 2011. Baseline characteristics were similar between groups with and without SR (Table 4). Patients ranged in age from 13 to 60 years, with a median age of 34 years. There were more male patients than female patients; however, the

Table 2 RIT protocol

Time	Dose (mL)	Dilution (v/v)
9:15 A.M.	0.05	1:10,000
9:30 A.M.	0.3	1:10,000
10:00 A.M.	0.1	1:1000
10:30 A.M.	0.3	1:1000
11:00 A.M.	0.1	1:100
12:00 P.M.	0.3	1:100
1:00 P.M.	0.1	1:10
2:00 P.M.	0.2	1:10

RIT = *rush immunotherapy*.

Table 3 Build-up schedule to the target dose after successful completion of the RIT protocol

Week	Dose (mL)	Dilution (v/v)
1	0.2	1:10
2	0.2	1:10
3	0.2	1:10
4	0.3	1:10
5	0.4	1:10
6	0.05	1:1
7	0.1	1:1
8	0.2	1:1
9	0.3	1:1
10	0.4	1:1
11	0.5	1:1

Increases occur weekly as listed.

RIT = *rush immunotherapy*.

proportion of male to female patients did not differ based on SR ($p = 0.21$). The number of allergens administered in the vaccines ranged from 3 to 47, with a maximum number of allergens per vial of 15 (Table 1). Seventy-two percent of patients (100 patients) had allergens divided into three different vials, 19% (26 patients) had two vials, 8% (11 patients) had one vial, and 0.7% (1 patient) had four vials.

SRs during RIT

One hundred thirty-eight patients received a total of 2911 injections. Of these, 38 patients (28%) had an SR during RIT. The SR rate per injection was 1.3%. Eighty-two percent of reactions (31 patients) occurred after the administration of the last RIT dose ($p < 0.001$). There were no SRs with doses lower than 0.3 mL 1:100 v/v. The majority of patients experienced grade 2 reactions (Table 5), which was similar to the reaction severities observed in our traditional IT patients (data not shown). Two patients experienced delayed reactions (>60 minutes after protocol completion); one patient developed chest tightness later that evening, which

was self-treated with albuterol and the other patient developed urticaria 2 hours after the last injection. No patients experienced grade 4 reactions or required emergency support or hospitalization. There was no association between the number of vials per person and risk of SR ($p = 0.38$).

SRs during RIT in Asthmatic Subpopulation

Thirty asthmatic patients received a total of 672 injections. Of these, seven patients (23%) had SRs (1% per injection). There was no difference in the morning PEFR of asthmatic patients who had SRs and those that did not ($p = 0.26$). The average FEV₁/forced vital capacity ratio was $79.9 \pm 7.3\%$. FEV₁ ranged from 71–113% with an average FEV₁ of $92 \pm 12\%$. There was no significant difference in the FEV₁ of patients with and without SR ($p = 0.87$).

SRs Post-RIT

Of the 138 RIT patients, 23 subsequently transferred care to another clinic for convenience purposes. Of the remaining 115 patients, 16 (14%) developed an SR during the post-RIT period. There was one SR at the first post-RIT dose, and this patient had not experienced an SR during RIT. There were no SRs at the second or third post-RIT doses. The post-RIT SR rate was 0.45% per injection, which is within the published range for traditional IT.⁵ Patients who experienced SRs during RIT were not at increased risk of having an SR post-RIT ($p = 0.226$). Most of the post-RIT reactions were grade 1 (Table 5).

Adherence

Between January and December 2008, there were 41 new RIT patients and 102 new traditional IT patients at our clinic. Sixty-one percent of RIT patients were still on IT as of February 2011 versus 46% of traditional IT patients ($p = 0.154$). Of the traditional IT patients who had dropped out, the majority (60%) quit during the build-up phase.

DISCUSSION

Over the past 100 years, aeroallergen IT has proven to be an effective treatment for allergic rhinitis. A major challenge facing allergists today is reducing the inconvenience of IT (*e.g.*, frequency of injections, travel time, and wait time) while maintaining its relative safety. Because most of the inconvenience occurs during the initial build-up, schedules such as RIT have been developed to accelerate this phase. Another potential benefit is decreasing the time to symptomatic improvement. Because of its elevated risk of SR compared with traditional IT, modifications such as premedication have been used to improve its safety. There has also been a trend to stop aeroallergen RIT protocols before

Table 4 Patient demographics and baseline characteristics

Subjects (n =140)	No SR (n = 100)	SR (n = 38)	Combined (n = 138)	p Value
Demographics				
Average age (yr; range, 13–60 yr)	34 ± 10	36 ± 11	34 ± 10	0.53
Gender				0.21
Female	40 (40%)	19 (50%)	59 (43%)	
Male	60 (60%)	19 (50%)	79 (57%)	
Medications				
H ₁ -receptor blocker	95 (94%)	38 (100%)	132 (96%)	0.12
INCS	83 (83%)	31 (82%)	114 (83%)	0.88
Montelukast	12 (12%)	7 (18%)	19 (14%)	0.19
ICS	17 (17%)	6 (16%)	23 (17%)	0.99
Intranasal antihistamine	37 (37%)	13 (34%)	50 (36%)	0.71
ACEI	2 (2%)	3 (8%)	5 (4%)	0.10
Comorbid conditions				
Asthma	23 (23%)	7 (18%)	30 (22%)	0.68
Chronic sinusitis	29 (29%)	10 (26%)	39 (28%)	0.93
Nasal polyps	10 (10%)	1 (3%)	11 (8%)	0.29
CIU	5 (5%)	2 (5%)	7 (5%)	0.97
Atopic dermatitis	3 (3%)	0 (0%)	3 (2%)	0.56
AFS	2 (2%)	0 (0%)	2 (1%)	1.00

SR = systemic reaction; H₁ = histamine 1; INCS = intranasal corticosteroid; ICS = inhaled corticosteroid; ACEI = angiotensin converting enzyme inhibitor; CIU = chronic idiopathic urticaria; AFS = allergic fungal sinusitis.

Table 5 SR during and post-RIT

SR Grade	RIT (n = 38)		Post-RIT (n = 16)	
	Immediate* Reaction	Delayed# Reaction	Immediate Reaction	Delayed Reaction
3	9 (23%)	0 (0%)	1 (6%)	1 (6%)
2	16 (42%)	1 (2.6%)	3 (19%)	1 (6%)
1	11 (28%)	1 (2.6%)	9 (56%)	1 (6%)

Source: Ref. 15.

*Immediate = <1 hr from time of injection.

#Delayed = >1 hr from time of injection.

SR = systemic reactions; RIT = rush immunotherapy.

the top maintenance dose because of the observation that the majority of SRs occur at the highest doses of the maintenance vial. Despite these modifications, SR rates have continued to be greater than those seen with traditional IT.

Most of the aeroallergen RIT protocols published have used single allergens. To our knowledge, two studies have been published using multiple mixed aeroallergens. The first by Sharkey *et al.* in 1996 reported an SR rate of 23% per person using 3 days of premedication and a protocol that ended at a low dose of the maintenance vial.⁴ In 2004, Harvey *et al.* tried to duplicate their experience with a larger sample size

and 2 days of premedication.⁵ The authors observed a high SR rate early in the study, which prompted them to decrease the final dose of the protocol further. They reported an SR rate of 38% per person, with the majority of reactions occurring with the highest doses.

Given their observations, as well as others, we developed a modified multiple aeroallergen RIT protocol that ends at one 10-fold dilution below the maintenance vial.^{15,17,18} We hypothesized decreasing the last dose of RIT to the 1:10 v/v dilution would decrease the SR rate closer to that seen with traditional IT, while still accelerating the patient through >50% of the build-up phase. Our observed SR rate was 28% per person (1.3% per injection). Although this is within the lower range for multiple aeroallergen RIT (23–73%), we did not observe rates as low as traditional IT. Like others, we observed that the majority of SRs occurred with the highest dose of our protocol. It remains unclear whether this occurs from the strength of the final dose or because of an accumulative effect of all the doses given over several hours.

The total time to reach the maintenance dose was 11 weeks. Because others have found a high reaction rate at the first post-RIT dose, our protocol repeated the final dose (0.2 mL 1:10 v/v) for 3 weeks before continuing to build.⁵ Only one patient experienced an SR at the first post-RIT dose, which suggests that it may be safe to proceed with the build-up more quickly, poten-

tially reaching the maintenance dose in 7–8 weeks. Additionally, because there were no reactions below 0.3 mL of 1:100 v/v, it may be safe to start at a higher dose, potentially decreasing the total number of RIT injections. The majority of patients selected for RIT were relatively young, healthy individuals. We did not observe a relationship between baseline FEV₁ or PEFR and risk of SR, likely because of patient selection, because 81% of asthmatic patients had a baseline FEV₁ > 80%.

The reasons why patients discontinue IT before the recommended length of treatment are varied, but among them include inconvenience and frequency of injections during the build-up phase. Although this study was not powered to detect differences in 2–3 years adherence, there may be a trend to improved adherence in the RIT group compared with traditional IT. Larger studies are needed to adequately evaluate the effects of accelerated IT schedules on patient adherence. Additionally, confounding factors that may affect adherence, such as patient satisfaction and cost-effectiveness, still have to be largely explored.¹⁹

The findings of our study raise the question whether multiple aeroallergen RIT has an acceptable place in clinical practice. Decreasing the ending dose of the protocol further would eliminate the benefit of being an “accelerated” process. Alternatively, aeroallergen cluster schedules have been associated with the same or increased risk of SR compared with traditional IT and may be safer.⁶ However, most of the safety data with cluster use single allergens, and the risk with multiple aeroallergens is unknown. Additionally, cluster schedules consists of four to six clusters of injections over several weeks, which may be impractical for many adults and school-aged children.

In conclusion, the desire to progress IT quickly to achieve rapid clinical improvement has been a driving force behind accelerated IT protocols over the past several decades. Although it is now accepted to be safe for venom allergy, it still has not been mastered for inhalant allergies. Although it is clear that modifications such as premedication improve its safety substantially, it is still unclear whether SR rates similar to accelerated Hymenoptera schedules or traditional IT are achievable with multiple aeroallergen RIT.

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