

Improved immunotherapy with a rapid allergen vaccination schedule: a study of 137 patients

[Ear, Nose & Throat Journal](#), [Nov, 2003](#) by [William Smits](#), [Joseph T. Inglefield](#), [Kevin Letz](#), [Robert Lee](#), [Timothy J. Craig](#)

Abstract

Rapid allergen vaccination (RAV) is the updated term for what was previously called rush immunotherapy and rapid desensitization. RAV offers several advantages over traditional immunotherapy--that is, conventional allergen vaccination (CAV)--in terms of faster efficacy, better compliance, and cost-effectiveness. We used a 3-hour RAV protocol to treat 137 allergy patients. All patients were premedicated with either prednisone or prednisolone and an [H.sub.1] antihistamine. Following the RAV procedure, all patients resumed a CAV schedule. Only six patients (4.4%) experienced a mild systemic reaction to RAV, and five (3.6%) experienced a mild systemic reaction to CAV 14 to 77 days later. All six patients who reacted to RAV quickly responded to treatment--in most cases, subcutaneous epinephrine and/or nebulized albuterol--and were sent home after a short period of observation. Compliance rates at 3, 6, and 12 months were 96.4, 94.2, and 75.9%, respectively, which is an improvement over rates previously reported for patients undergoing CA V therapy. We conclude that the 3-hour RAV protocol can be safely and successfully administered. Patients who undergo RAV are more compliant with their subsequent CA V regimen than are patients who do not undergo RAV because signs of clinical efficacy manifest almost immediately and because RAV is associated with substantially lower rates of systemic reactions. Moreover, RAV is associated with less morbidity and less expense. Our findings should encourage physicians who treat allergy patients to give further consideration to using RAV.

Introduction

Allergen vaccination is effective in the treatment of allergic rhinitis, (1-4) allergic asthma, (5-11) and Hymenoptera allergy. (12,13) Conventional allergen vaccination (CAV) involves weekly inoculations of gradually increasing concentrations until a maintenance dose is reached. Thereafter, vaccinations are administered biweekly or monthly for 3 to 5 years. Ideally, the CAV protocol induces immunity and results in remission of disease. Measurable levels of immunoglobulin G4 following CAV therapy support the fact that it does alter the immune system. The mechanism of action appears to involve a decrease in type 2 T-helper cells and an increase in type 1 T-helper cells, which leads to a decrease in the expression of allergic disease.

However, inappropriate discontinuation of CAV by patients is common because compliance requires a long-term commitment and discipline. Patients will also discontinue therapy prematurely if they perceive that they are not obtaining any immediate benefit. Reports of compliance rates greater than 60% are unusual. (14,15)

Rapid allergen vaccination (RAV)--previously called rush immunotherapy and rapid desensitization--administered prior to CAV has several advantages over CAV alone. First, RAV should improve compliance, primarily because patients experience clinical efficacy more quickly than they do without it. More rapid efficacy also reduces morbidity. Finally, because RAV does not require up to 6 months of weekly "build-up" injections, both direct and indirect costs to the patient are reduced. By receiving a series of increasingly more concentrated immunizing doses, patients can achieve an effective maintenance dose in a period of just 1 to 7 days. (10,16,17)

The major controversy over RAV concerns its safety--specifically, the potentially higher risk of systemic reactions that could result in anaphylaxis or death. (18,19) Rates of systemic reactions to RAV have been reported to be greater than 15% in some studies, (17,20-24) and Portnoy et al reported a systemic reaction rate of 23%. (22) Reported rates of systemic reactions to CAV have varied greatly, from 0.8 to 46.7%. (23)

In this article, we describe our study of the safety of a practical RAV protocol for office-based physicians who treat patients with allergies.

Patients and methods

Patient selection. Our study population was made up of 137 patients--61 males and 76 females, aged 2 to 68 years--who were selected from the case load of an office-based allergy practice. All patients had at least one of the following conditions: allergic rhinitis (137 patients), allergic asthma (109), and chronic sinusitis (62); 64 of these patients also had sinusitis-associated headaches. Each was positive for immunoglobulin E (IgE) on percutaneous testing, and each had a history consistent with allergy-mediated disease. Exclusion criteria included a history of anaphylaxis, a forced expiratory volume in 1 second (FE[V.sub.1]) of less than 70% of predicted by pulmonary function testing, a history of cardiovascular disease, and current beta blocker use.

Percutaneous allergy testing. For allergy testing, we used 1:10 weight/volume (w/v) glycerinated extracts (Greer Laboratories; Lenoir, N.C.). The epicutaneous technique was performed with the DermaPik (Greer Laboratories). Intradermal tests were performed with the same allergen extract in a 1:2,000 dilution and administered by 25-gauge syringes. Tests were read 20 minutes after placement. Skin sensitivity was measured in millimeters of wheal and flare. Those whose percutaneous test results were negative underwent further intradermal testing to confirm IgE sensitivity. Individual scratch or intradermal tests were considered to be positive when either the wheal or flare was at least 5 mm larger than the negative diluent control.

Allergen vaccination extract. Vaccine extracts were prepared according to stock formulations used by Greer Laboratories. Both aqueous and glycerinated extracts were used to achieve a concentrate of 1:100 w/v of the mixed extract. Serial 10-fold dilutions of this concentrate were prepared so that the concentrate was identical to that used for CAV. To minimize systemic reactions, the targeted final dose during the RAV procedure was a 1:1,000

dilution. To reduce proteolytic degradation, separate vials were used for pollen and mold extracts. All extracts were stored at approximately 4[degrees] C. Serum varied with each individual patient; most patients' serum included a variety of aeroallergens, including mold, tree, grass, weed, mite, dust, cat, and dog allergens.

Procedure for RAV. The option to undergo RAV therapy was offered to all patients in the office practice whom we thought might benefit from immunotherapy. A registered nurse explained the potentially higher risks of RAV, including the risk of anaphylaxis, and written and signed informed consent was obtained from each of the 137 suitable candidates who accepted the offer. The procedure was scheduled 1 to 2 weeks later. Prior to RAV, a 3-day premedication regimen of a steroid and an antihistamine was prescribed. Patients younger than 5 years received either prednisone or prednisolone at 15 mg twice a day, those aged 5 to 12 years received 20 mg twice a day, and the rest received 30 mg twice a day. The [H.sub.1] antihistamines--cetirizine, fexofenadine, and loratadine--were prescribed at age-appropriate doses.

On the day of the procedure, each patient was reassessed by history, physical examination, and spirometry. Any documented clinical worsening (e.g., the presence of upper respiratory tract infection or a decrease in spirometric values) necessitated that the procedure be rescheduled. Patients received injections of a different volume and dilution every 15 minutes for 105 minutes (table 1). If a patient experienced a systemic reaction, the next dose usually was reduced by 10-fold; the patient then resumed the normal schedule. We did not alternate arms for injections. Patients who required two simultaneous injections (e.g., separated pollen and fungal allergens) received one in each arm. Patients were observed for 30 minutes after their final injection and sent home if they were stable. After the RAV procedure, patients resumed a CAV schedule.

Results

Systemic reactions to RAV. Systemic reactions occurred in 6 of the 137 patients (4.4%) between the second and final dose on the day of the RAV procedure (table 2). Five of the 6 had pre-existing asthma and were taking an inhaled corticosteroid; 4 were between the ages of 10 and 13 years (table 3). All 6 were treated and closely monitored by a trained physician or nurse for at least 60 minutes following the adverse event, and all were sent home within several hours. All but one continued their CAV regimen. All of the systemic reactions occurred within 15 minutes of the offending injection. Treatment usually included one or more of the following: subcutaneous epinephrine (1 mg/ml) at a dilution of 1:1,000, nebulized albuterol, two sprays in each nostril of azelastine, and diphenhydramine taken orally or intramuscularly. The extract composition in these patients included mold in 6, grass in 5, tree in 4, and weed in 4 (table 3).

Two patients with immediate systemic reactions were exceptional and deserve further discussion. Patient 60, a 29-year-old woman, had an atypical systemic reaction that might not have been allergic in nature. She experienced abdominal pain that caused her severe discomfort. She was treated with subcutaneous epinephrine, nebulized albuterol, and diphenhydramine and sent to the emergency department (ED) for observation. While in the ED, she later received methylprednisolone sodium succinate (125 mg), diphenhydramine (25 mg), ranitidine (50 mg), and ketorolac (30 mg), all intravenously. She said her reaction was similar to urinary bladder "spasms" that she often experienced.

Patient 62, a 10-year-old girl, had a systemic reaction (chest tightness) within 15 minutes of her fourth RAV injection and another reaction the next day; the day-2 reaction was characterized by nasal itching, cough, and headache. She was treated with prednisone (30 mg) for 3 days and recovered. She continued to receive CAV therapy, and she later experienced another systemic reaction on day 77, which is discussed later in this article.

Systemic reactions to CAV. Five patients (3.6%), including patient 62, experienced a systemic reaction to CAV within 3 months (table 4). On day

77, patient 62 experienced chest tightness and shortness of breath almost immediately after receiving a weekly allergen vaccination. She was treated in the office and sent home within an hour of the reaction.

All 5 patients who experienced a reaction to CAV completed their vaccination schedule without any further complications. Patient 5, a 48-year-old woman, experienced slight chest tightness approximately 2 hours after she received a weekly allergy injection on day 60. No treatment was necessary.

Patient 8, a 29-year-old man, complained of tightness in the throat, heaviness in the chest, and urticaria on day 41 after he received his weekly allergen vaccination at work. The nurse at his workplace treated him with 25 mg of diphenhydramine, and he felt better soon thereafter.

Patient 55, a 16-year-old girl, called the office approximately 2 hours after she had received a weekly allergen vaccination on day 29 and complained of a rash that started on her neck and spread to her stomach. She experienced no respiratory problems. Her rash resolved after treatment with an antihistamine and 30 mg of prednisone, and she continued immunotherapy without any further complications.

Patient 116, a 29-year-old woman, received her first weekly injection following RAV without incident. However, 1 week later, she experienced a systemic reaction after receiving her second weekly injection at an urgent care center. According to the records of the urgent care office, she developed urticaria approximately 1 hour after the injection. She returned to the urgent care center and received an intramuscular injection of diphenhydramine. Her systemic reaction completely subsided within 10 minutes.

Build-up period. After the RAV procedure, patients typically required at least 2 more months of build-up to achieve their targeted maintenance dose.

Compliance. At 3 months, 132 of the 137 patients (96.4%) were still following their CAV schedule. At 6 months, 129 patients (94.2%) were still

following their regimen, and at 12 months, 104 patients (75.9%) remained compliant.

Discussion

Advantages of RAV. CAV is often viewed by patients and referring physicians as an inconvenient procedure that can take a year or more to become effective. (14,15) Therefore, a strategy that improves efficacy while maintaining safety would be a welcome addition to the armamentarium. RAV is a promising alternative. Moreover, the enhanced efficacy is cost-effective. In a position paper published in 1998, the World Health Organization stated that "over the past 10 years, costs for asthma and allergic diseases have increased more than for most other diseases." (25) Clearly, it is imperative that we continue to look for ways to decrease the costs of care for our patients. Patients who choose to undergo RAV can avoid the build-up period that stretches up to 6 months for some patients. With RAV, the cost of therapy can be reduced by as much as 50% during the first year because 24 weekly vaccinations will not be necessary.

In turn, a less complex and less expensive treatment can improve patient compliance. Studies have shown that inconvenience is the primary reason for high drop-out rates. (14,15,26) Our 12-month adherence rate of 75.9% compares favorably with compliance rates for CAV reported by Cohn and Pizz (14) (50%) and by Lower et al (15) (56%). Other possible advantages to RAV are less morbidity, less need for medication, and fewer ED visits and hospitalizations.

Complication rates. High rates of systemic reactions associated with RAV in previous studies have discouraged its use. (17,19,21-23) We found that by carefully selecting appropriate patients and by premedicating them, we greatly reduced the risk of systemic reactions. (27,28) The rates of systemic reactions during RAV (4.4%) and CAV (3.6%) in our study are at the low end of the range reported for CAV (0.8 to 46.7%). (23) Nevertheless, most allergists agree that the higher rates reported in CAV studies far exceed the

rates seen in office practice; those higher rates are unacceptable in office practice.

Even so, the primary reason for our low rate of complications was that our targeted endpoint dose was low. In previous studies, high rates of systemic reactions were associated with high doses. (24) By reducing the doses, we lowered the risk of systemic reactions. Our targeted endpoint dose was one-tenth the dose targeted by Sharkey and Portnoy. (24) In fact, had we reduced the dose 100-fold, our rate of systemic reactions might have been halved because patients 21, 60, and 65 all reacted to the most concentrated vial (1:1,000 dilution).

Observation period. Only one of the six patients who had a systemic reaction during the RAV protocol (patient 62) reported difficulty beyond the 30-minute observation period that we required for all patients. Patient 62 experienced chest tightness within 15 minutes of her fourth injection on day 1 and nasal itching, cough, and headache 1 day later. The 10-year-old girl also experienced chest tightness and shortness of breath following an injection on day 77 of therapy. The other five patients who experienced a systemic reaction on day 1 all did so within 15 minutes of the offending injection. The American College of Allergy, Asthma, and Immunology recommends approximately 20 minutes of observation for patients who undergo CAV and longer for patients who are at higher risk for complications, (29) which includes RAV patients. (23) We recommend an observation period of 30 minutes.

Age. Age might be an important risk factor for systemic reactions. Of the six patients in our study who experienced reactions to RAV, four (66.7%) were 13 years of age or younger. However, this age group accounted for only 26.3% (36/137) of the total number of patients in our study. We are unable to explain the association. We do know that children are less compliant than adults when taking oral medications, (26,30) so perhaps closer scrutiny of their adherence to the premedication regimen would have been wise. (30-32)

We conclude that a 2- to 3-hour RAV protocol with premedication is a safe and effective procedure for selected patients with allergic rhinitis, allergic asthma, chronic sinusitis, and associated headache. Patients who undergo this procedure are able to reach an effective maintenance dose more quickly than do those who undergo CAV alone. Of course, caution and good clinical judgment must be exercised when selecting suitable candidates for therapy.

Table 1. RAV dosing schedule

Time (min)	Volume (ml)	Dilution
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	1:1,000
105	0.1	1:1,000

Table 2. Description and treatment of systemic reactions to RAV

Pt. no.	Age/ sex	Reaction	Time to reaction	Reaction dose
21	11/F	Headache	5 min	0.025 ml of 1:1,000
60	29/F	Abdominal pain	5 min	0.1 ml of 1:1,000
62	10/F	Chest tightness	15 min	0.25 ml of 1:100,000

65	31/M	Dizziness, itchy hands	15 min	0.1 ml of 1:1,000
68	11/M	Throat tightness, cough	15 min	0.25 ml of 1:100,000
97	13/M	Cough, shortness of breath	5 min	0.025 ml of 1:100,000

Pt. no.	Treatment	Late reaction
------------	-----------	------------------

21	Acetaminophen	No
----	---------------	----

60	Subcutaneous epinephrine (1:1,000), nebulized albuterol, diphenhydramine (25 mg)	No
----	--	----

62	2 sprays of pirbuterol, 2 sprays of azelastine, nebulized albuterol, prednisone (30 mg)	Yes
----	---	-----

65	Subcutaneous epinephrine (1:1,000), 2 sprays of azelastine	No
----	---	----

68	Subcutaneous epinephrine (1:1,000), nebulized albuterol	No
----	--	----

97	Diphenhydramine, subcutaneous epinephrine (1:1,000), nebulized albuterol	No
----	--	----

Table 3. Characteristics of patients who experienced systemic reactions to RAV

Patient no.	21	60	62	65	68	97
Age/sex	11/F	29/F	10/F	31/M	11/M	13/M
Symptoms						
Rhinitis	Yes	Yes	Yes	Yes	Yes	Yes
Asthma	Yes	Yes	Yes	No	Yes	Yes
Chronic sinusitis	No	No	Yes	No	No	No
Headache	No	Yes	Yes	No	Yes	Yes
Allergens						
Mold	Yes	Yes	Yes	Yes	Yes	Yes
Grass	Yes	Yes	Yes	Yes	No	Yes
Tree	Yes	Yes	No	Yes	No	Yes
Weed	Yes	Yes	No	Yes	No	Yes
Dust	No	No	No	No	Yes	Yes
Cat	No	No	No	No	Yes	Yes
Dog	No	No	No	No	No	Yes
Mite	No	No	No	No	Yes	No

Table 4. Description and treatment of systemic reactions to CAV

Pt. no.	Age/sex	Reaction	Time to reaction	Treatment
5	48/F	Chest tightness	60 days	None (self-limited)
8	29/M	Throat tightness, chest heaviness, urticaria	41 days	Diphenhydramine (25 mg)

55	16/F	Neck and stomach rash	29 days	Diphenhydramine (25 mg), prednisone (30 mg)
62	10/F	Chest tightness, shortness of breath	77 days	Nebulized treatment, prednisone (30 mg)
116	29/F	Urticaria	14 days	Diphenhydramine (25 mg)

References

- (1.) Creticos PS. Immunotherapy with allergens. JAMA 1992;268: 2834-9.
- (2.) McHugh SM, Lavelle B, Kemeny DM, et al. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssinus* in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol 1990;86(Pt 1):521-31.
- (3.) Norman PS, Van Metre TE, Jr. The safety of allergenic immunotherapy. J Allergy Clin Immunol 1990;85:522-5.
- (4.) Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: An analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. Clin Ther 2000;22:342-50.
- (5.) Bousquet J, Michel FB. Specific immunotherapy in asthma: Is it effective? J Allergy Clin Immunol 1994;94:1-11.
- (6.) Cantani A, Businco E, Benincori N, et al. A three year controlled study in children with pollinosis treated with immunotherapy. Ann Allergy 1984;53:79-84.

(7.) Cantani A, Arcese G, Lucenti P, et al. A three-year prospective study of specific immunotherapy to inhalant allergens: Evidence of safety and efficacy in 300 children with allergic asthma. *J Investig Allergol Clin Immunol* 1997;7:90-7.

(8.) Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: Clinical efficacy and side effects. *J Allergy Clin Immunol* 1993;91:709-22.

(9.) Mailing HJ. [Allergen-specific immune therapy in the treatment of asthma]. *Ugeskr Laeger* 2000;162:477-9.

(10.) Nagata M, Yamamoto H, Tabe K, et al. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: Changes in in vivo and in vitro responses to HDM. *Intern Med* 1993;32:702-9.

(11.) Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: A meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther* 2000;22:329-41.

(12.) Bernstein DI, Mittman RJ, Kagen SL, et al. Clinical and immunologic studies of rapid venom immunotherapy in Hymenopterasensitive patients. *J Allergy Clin Immunol* 1989;84(Pt 1):951-9.

(13.) Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: A meta-analysis. *Clin Ther* 2000;22:351-8.

(14.) Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993;91:734-7.

(15.) Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. *Ann Allergy* 1993;70:480-2.

(16.) Bousquet J, Calvayrac P, Guerin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734-44.

(17.) Hejjaoui A, Ferrando R, Dhivert H, et al. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;89:925-33.

(18.) Bousquet J, Guerin B, Dotte A, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. *Clin Allergy* 1985;15:179-93.

(19.) Sundin B, Lilja G, Gruff-Lonnevig V, et al. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol* 1986;77:478-87.

(20.) Bousquet J, Hejjaoui A, Dhivert H, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol* 1989;83:797-802.

(21.) Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol* 1990;85:473-9.

(22.) Portnoy J, King K, Kanarek H, Homer S. Incidence of systemic reactions during rush immunotherapy. *Ann Allergy* 1992;68: 493-8.

(23.) Stewart GE II, Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol* 1992;90(Pt 1):567-78.

(24.) Sharkey P, Portnoy J. Rush immunotherapy: Experience with a one-day schedule. *Ann Allergy Asthma Immunol* 1996;76: 175-80.

(25.) Allergen immunotherapy: Therapeutic vaccines for allergic diseases. Geneva: January 27-9, 1997. Allergy 1998;53(Suppl):1-42.

(26.) Wynn SR. Immunotherapy compliance--a shot in the dark? Ann Allergy Asthma Immunol 1995;74:195-7.

(27.) Nielsen L, Johnsen CR, Mosbech H, et al. Antihistamine pre-medication in specific cluster immunotherapy: A double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97:1207-13.

(28.) Portnoy J, Bagstad K, Kanarek H, et al. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. Ann Allergy 1994; 73:409-18.

(29.) The waiting period after allergen skin testing and immunotherapy. American Academy of Allergy and Immunology. J Allergy Clin Immunol 1990;85:526-7.

(30.) Tinkelman D, Smith F, Cole WQ III, Silk HJ. Compliance with an allergen immunotherapy regime. Ann Allergy Asthma Immunol 1995;74:241-6.

(31.) Weinstein AG. Asthma treatment and noncompliance. Del Med J 2000;72:209-13.

(32.) Weinstein AG. Clinical management strategies to maintain drug compliance in asthmatic children. Ann Allergy Asthma Immunol 1995;74:304-10.

From the Allergy and Asthma Center, Fort Wayne, Ind. (Dr. Smits and Dr. Letz), the Hickory (N.C.) Allergy and Asthma Clinic (Dr. Inglefield), the Indiana University School of Medicine, Indianapolis (Mr. Lee), and the Department of Pulmonary Allergy and Critical Care Medicine, Pennsylvania State University College of Medicine, Hershey (Dr. Craig).

Reprint requests: William Smits, MD, Allergy and Asthma Center, 7230 Engle Rd., Suite 300, Fort Wayne, IN 46804-2234. Phone: (260) 432 5005; fax: (260) 432-6003; e-mail: wlsmits@aol.com

Originally presented at the annual meeting of the American College of Allergy, Asthma, and Immunology; Nov. 19, 2001; Orlando, Fla.