

Safety and efficacy of radioallergosorbent test-based allergen immunotherapy in treatment of perennial allergic rhinitis and asthma

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OBJECTIVE: This study was undertaken to demonstrate the safety and efficacy of in vitro, radioallergosorbent test (RAST)-based inhalant allergen immunotherapy.

STUDY DESIGN AND SETTING: Prospective 22 year single site clinical study, with outcome evaluations of 480 perennial allergic rhinitis patients, including 96 with concomitant asthma.

RESULTS: Rhinitis symptom control after 2 years of immunotherapy was excellent in 32.5% of patients, good in 45.6%, and fair in 14.2%. There was no improvement in 7.7%. For patients with asthma, 81% had good or excellent pulmonary symptom improvement, and no patient failed to improve. No severe reactions occurred, but there were 5 limited systemic reactions, or 0.008% of injections, during a 2.5-year mean immunotherapy treatment course.

CONCLUSION: RAST-based immunotherapy is safe and effective for patients with perennial allergic rhinitis, with or without concomitant asthma.

SIGNIFICANCE: This is the first large, multiyear study of safety and efficacy of RAST-based immunotherapy for treatment of perennial allergic rhinitis and asthma. **EBM rating:** C. (Otolaryngol Head Neck Surg 2004;131:673-8.)

Allergic rhinitis is a common worldwide disease that significantly impairs a patient's quality of life.^{1,2} During the last few years, international guidelines have recommended that the management of allergic rhinitis include a step care approach of allergen avoidance, pharmacological treatment, and immunotherapy.³⁻⁸ Al-

lergen immunotherapy is the administration of gradually increasing quantities of allergen extracts to an allergic subject, ultimately reaching a dose range that is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergens. In 1998, a World Health Organization position paper stated that immunotherapy was the only treatment that might affect the natural course of allergic diseases, and it also might prevent the subsequent development of asthma in allergic rhinitis patients.⁷ However, in many allergic rhinitis patients, allergic asthma is already a clinical problem at the time of initial treatment. Thus, evaluation of treatments for allergic rhinitis should also include assessment of the treatment effects on asthma, when this is present.

A major clinical decision when using immunotherapy is to identify safe initial treatment doses. In vitro testing, using the modified radioallergosorbent test (RAST) scoring system, is a dependable method for the determination of initial immunotherapy doses.⁹ A major advantage of this technique is that it allows the physician to select initial immunotherapy doses that are as concentrated as possible, but still safe, by using the modified RAST (mR) classes as accurate indicators of allergen-specific IgE levels in each patient. Because RAST testing quantifies specific IgE levels for each allergen, the physician can select safe initial immunotherapy doses for each antigen independently. When the degree of sensitization is low to moderate, immunotherapy is started at high allergen concentrations, thereby reducing the time and number of injections needed until effective doses are achieved. When high sensitivity exists, immunotherapy is started at appropriately cautious low allergen concentrations. When sensitivity to different antigens varies significantly, mR class results can be used to select initial treatment doses for each antigen in inverse proportion to the identified degree of sensitivity. Immunotherapy can then be advanced without the risk of reactions caused by high sensitivity allergens preventing the advancement of low sensitivity allergen treatment. This paper summarizes our experience with immunotherapy in a large number of patients with RAST-determined, IgE-mediated allergy.

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Presented at the Annual Meeting of the American Academy of Otolaryngic Allergy, San Diego, CA, September 20, 2002.

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0194-5998/\$30.00

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doi:10.1016/j.otohns.2004.04.020

Table 1. RAST-based initial immunotherapy doses

Modified RAST class	IgE IU/mL	Allergen concentration (w/v) for initial treatment
0	Negative	No treatment
1	0.08–0.15	1:2,500
2	0.15–0.50	1:12,500
3	0.50–2.50	1:62,500
4	2.50–12.5	1:312,500
5	12.5–62.5	1:1,562,500

MATERIALS AND METHODS

Patients and Testing

During 1978 to 2000, 480 patients with perennial allergic rhinitis, with or without asthma, were treated with immunotherapy at the ENT and Allergy Clinic, Singapore. Ninety-six patients had concomitant asthma (20%), and 10 had eczema (2%). There were 336 males and 144 females, aged from 4 years to 62 years (mean age, 22.9 years). Each person's degree of reactivity to common tropical inhalant allergens was measured by mR, using a Hycor PSP 5052, with Hytec CE-version 1.0 software (Tecan Group Ltd., Seestrasse 103, Maennedorf, Switzerland, CH-8708). In vitro results were reported as classes 0, 0/1, and 1 to 5. For this report, results of 0/1 and 0 were combined. The test panel included: *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), Bermuda grass (*Cynodon dactylon*), *Aspergillus fumigatus*, short ragweed (*Ambrosia artemisiifolia*), cockroach (*Blattella germanica*), and dog and cat, if patients had these pets at their home. All patients were educated with detailed information about immunotherapy, including benefits and risks, and a verbal consent for treatment was obtained from each.

Allergen Extracts

For each patient, all antigens with a positive mR result of class 1 or greater were treated, provided that at least 1 antigen was mR class 3 or greater. For patients with a positive mR to both Der p and Der f, both mites were treated. Immunotherapy antigens for each patient were combined in a single treatment vial, which was refrigerated, and outdated after a maximum of 4 months. Commercial allergen extracts, 1:20 weight/volume in 50% glycerin (Meridian/ALK-Abello, Inc., 1700 Royston Lane, Round Rock, TX), were sequentially diluted 5-fold with phenolated normal saline to prepare solutions from which immunotherapy treatment vials would be made (Table 1). For all antigens in which standardized allergen extracts have replaced nonstandardized

extracts, standardized allergens were used at the highest available concentration.

Immunotherapy Treatment

The initial treatment dose for each reactive antigen was prepared at an antigen concentration corresponding to 2 dilutions less concentrated than the specific mR class for each antigen (Table 1). Patients were routinely advised to avoid their positive allergens, and especially to eliminate house dust from their living environments. Patients were observed at a medical office for at least 30 minutes following every allergen injection. However, a longer waiting period was required for patients who showed any early signs or symptoms of adverse reaction. In all cases, before initiating treatment from a new treatment vial, a 0.01-mL intradermal safety vial test injection was performed.

One week after an acceptable sized vial test, an initial 0.05 mL treatment dose was given subcutaneously, then escalated by 0.05 mL for the second dose, and then by 0.1 mL at weekly intervals to reach 0.5 mL. Escalation was then continued with treatment vial 2, 5-fold more concentrated, then with vial 3, 25-fold more concentrated than the first vial, until symptoms were relieved, or a dose of 0.5 mL from vial 3 was reached. Upon reaching this usual maximum dose, the few patients without a treatment response were evaluated for other possible allergies, including food allergies, and, in some instances, further dose escalation was performed until the optimal maintenance dose was determined. In patients who had not yet reached the expected maximum dose, but developed a large local reaction >25 mm in diameter, the dose was temporarily reduced to previously tolerated levels. If repeated attempts to advance the dose further were unsuccessful, the maximum dose producing less than a 25-mm zone of induration was used as the maintenance dose. Weekly treatment was continued for from 1.5 to 2 years, and then the interval was usually extended to 2 weeks if the patient continued to do well. Immunotherapy was normally stopped after 3 to 5 years.

Symptom Response Assessment

Histories of allergic and all other medical symptoms were obtained from each patient at the initial visit, and complete head and neck examination was performed. Diagnoses of asthma and eczema were confirmed by pulmonary or dermatology specialists. Presence and severity of up to 4 major allergic rhinitis symptoms were recorded for each patient and entered into a computer database. Most patients had typical symptoms including obstruction (76%), rhi-

Table 2. Percent of positive RAST test results for each allergen in rhinitis patients, by sensitivity class (n = 480, 100%)

Tested allergen	Modified RAST class					
	0	1	2	3	4	5
Der p	3	2	5	11	41	38
Der f	5	1	5	11	38	40
Bermuda grass	50	22	15	6	5	2
Aspergillus flavus	71	22	6	1	0.2	0
Cockroach	64	21	10	4	1	0.2
Short ragweed	96	2	0.6	1	0.4	0.2
Dog*	30	15	27	15	12	0
Cat†	26	7	19	13	25	10

*n = 66 patients tested.

†n = 31 patients tested.

norrhea (66%), sneezing (45%), itchy eyes (12%), and cough (11%). Follow-up evaluations were scheduled at 3-month intervals. During each visit, patients were asked to assess the combined percent improvement in all of their major allergic symptoms. More than 70% improvement was rated as excellent, 50% to 70% as good, less than 50% as fair, and 0% as none. Asthma symptoms were separately evaluated, using the same rating scale. Dropouts, patients who completed less than 6 months of build up, or less than 2 years of total immunotherapy with no improvement, were counted as immunotherapy failures.

Data Analysis

Statistical tests were carried out 2-tailed at the 5% level of significance. The calculations were performed using SPSS/PC for Windows, release 10. 0.5 (SPSS Science, Chicago, IL). The χ^2 test was used to evaluate the relationship between symptom improvement and duration of immunotherapy treatment, and the relationship of high mR classes for dust mites to degree of symptom improvement.

RESULTS

Incidence of Allergic Sensitivity

Atopy to house dust mites was the most prevalent finding, with a positive mR class in 98% of patients (Table 2), followed by Bermuda grass, with 50% of tests positive. *Aspergillus fumigatus* and German cockroach were each positive in approximately one third of patients, and other allergens tested positive only rarely. Thirty-six percent of patients had only 1 positive RAST test, 24% were positive to 2 allergens, 16% to 3 allergens, and 24% were sensitive to more than 3 antigens. Most mR classes were low (class 1 or 2), except for mites, for which more than three fourths of patients were high sensitivity (class > 4), and the mean mR class for both mite species was 4.2.

The sensitivity pattern for asthmatics (Table 3) was almost identical to that for the entire population, but with an even greater prevalence of high sensitivity mite allergy.

Clinical Response

Table 4 shows that 78% of patients showed good or excellent rhinitis symptom improvement, whereas 7.7% of patients, including dropouts, did not respond to immunotherapy treatment. Among the subset of patients with asthma, all 96 patients had improved pulmonary symptoms, and 81% were good or excellent (Table 5).

Treatment Dropouts

Twenty-six patients (5.4%) dropped out of treatment. The reason for discontinuing treatment was most often because of inability to follow the treatment schedule. Treatment results, at the time of stopping immunotherapy, were fair in 8, good in 12, and excellent in 2. Patients who stopped treatment all had antigen sensitivities similar to those of patients who continued with treatment. Of these 26 patients, 4 had no apparent therapeutic benefit before they stopped treatment, but 1 patient restarted treatment after an 8-month lapse because his asthma, but not his rhinitis, did improve on immunotherapy.

Duration of Therapy

The duration of immunotherapy (Table 4), for all patients, ranged from 3 months to 10 years (mean, 2.49 years). There was a highly significant ($P = 0.0001$) relationship between degree of rhinitis symptom improvement and duration of immunotherapy. Most patients with no, or only fair, improvement stopped immunotherapy treatment in less than 2 years, whereas patients with more improvement continued with immunotherapy for up to 10 years

Table 3. Percent of positive RAST test results for each allergen in asthma patients, by sensitivity class (n = 96, 100%)

Tested allergen	Modified RAST class					
	0	1	2	3	4	5
Der p	3	2	3	5	28	58
Der f	3	3	3	6	28	56
Bermuda grass	48	20	22	5	2	3
Aspergillus flavus	64	29	6	1	0	0
Cockroach	54	29	11	5	1	0
Short ragweed	97	1	1	0	0	1
Dog	77	6	9	5	3	0
Cat	88	0	0	6	6	0

Table 4. Rhinitis symptom improvement and mean duration of immunotherapy (n = 480, combined mean = 2.49 years)

Symptom improvement	Patients (%)	Immunotherapy mean duration (y)
None	37 (7.7)	1.40
Fair	68 (14.2)	1.63
Good	219 (45.6)	2.18
Excellent	156 (32.5)	3.57

Table 5. Asthma symptom improvement and mean duration of immunotherapy (n = 96, combined mean = 2.86 years)

Symptom improvement	Patients (%)	Immunotherapy mean duration (y)
None	0 (0)	–
Fair	18 (19)	1.4
Good	41 (43)	2.5
Excellent	37 (38)	3.9

before they were willing to discontinue injections. It is known that immunotherapy results continue to improve for several years,¹⁰ but, it is equally likely that patients who were having greater benefits were more inclined to continue with therapy, despite its financial impact and inconvenience.

Antigen Sensitivity

Table 6 shows that patients with house dust mite allergy of all degrees of sensitivity respond equally well to immunotherapy treatment. There was a nonsignificant trend ($P = 0.08$) for patients with high dust mite mR classes > class 4 to have a higher percentage of good or excellent symptom improvement. The small minority of patients reacting to only non-mite allergens

had similar improvement to those with dust mite allergy. Three of 14 were nonresponders, 1 had a fair response, and 10 (71%) had good or excellent therapeutic results.

Treatment Side Effects

Immunotherapy side effects were infrequent. Less than 5% of patients developed large local reactions exceeding 2.5 cm at the injection site. These all responded to dose reduction. Limited systemic reactions occurred in 5 patients (1%) between 20 and 60 minutes after injection (Table 7), 1 during the build-up phase, and 4 at the beginning of maintenance dose treatment. Three of the 5 patients were asthmatic. There were no other risk factors identified. All patients recovered after office medical treatment. Three patients were each treated with 1 injection of subcutaneous epinephrine and 1 injection of intramuscular hydrocortisone. The other 2 patients received only an oral antihistamine. This is a rate of systemic reactions per injection of 1 in 12,400, or 0.008%, which is a low rate, substantially better than most other reports, and comparable with reports in which immunotherapy is based on quantitative testing methods.¹¹ These 5 patients all continued their immunotherapy after a decrease in their treatment doses, and had no further reactions.

DISCUSSION

Immunotherapy is one of the main treatment options for IgE-mediated inhalant allergy. Allergens for which immunotherapy has proven to be effective include tree, grass, and weed pollens; house dust mites; cat, and molds.⁸ There have been over 43 double-blind, placebo-controlled studies of immunotherapy for allergic rhinitis, with a mean reduction of symptom or medication scores of 45% above the level of placebo effects.¹² Immunotherapy has also proven effective in treatment of asthma.¹³

We have previously reported that perennial rhinitis is the most prevalent type of rhinitis in Singapore,¹⁴

Table 6. Symptom improvement by specific IgE level in patients with dust mite allergy (n = 466)

Modified RAST class	Patients	Degree of Symptom Improvement			
		None	Fair	Good	Excellent
1	8	2	0	5	1
2	15	2	3	4	6
3	35	5	2	19	9
4	159	12	22	73	52
5	249	13	40	109	87

Table 7. Symptoms observed during systemic reactions occurring in 5 of 480 immunotherapy patients

Symptoms	Number of patients (n = 5)	Time after injection (min)
Urticaria or rash	5	20–60
Chest tightness	3	30–60
Throat tightness	1	20
Periocular edema	1	30

where, because of the tropical climate, house dust mites are the most common aeroallergen.¹⁵ Because patients with perennial allergies must be treated during the entire year, data from this current study are important, bearing on choice of treatment decisions, and the subsequent effects on both patient outcomes and costs of therapy. Immunotherapy has been considered by some to be more likely to be effective for patients who are allergic to seasonal allergens than for those who have chronic nasal disease as a result of perennial allergens.⁷ But, there is scant data on the efficacy of immunotherapy in patients with perennial allergic rhinitis, especially that as a result of persistent house dust mite exposure. In 1 of the few publications, Ohashi et al¹⁶ have shown that long-term mite immunotherapy is superior to pharmacologic treatment, especially for chronic nasal congestion relief. Perennial mite allergies have also been strongly incriminated in causation of tropical asthma attacks.¹⁷

The current immunotherapy study included 480 patients, 384 with only perennial allergic rhinitis, and 96 with both perennial rhinitis and asthma. House dust mite sensitivity was present in 98% of these patients, and was the primary allergic problem for most. At 2 years into their immunotherapy treatment, 78% of these patients showed greater than 50% rhinitis symptom reduction, and patients with all degrees of mite sensitivity benefited from treatment. Also, 81% of patients with concomitant asthma had a similarly high degree of pulmonary symptom improvement. There was a trend

($P = 0.08$) for patients with mite mR classes greater than class 4 to have a higher percentage of good or excellent symptom improvement. This is an expected result, because more than three fourths of patients had a mite mR class of greater than class 4, and therefore were receiving maintenance immunotherapy doses within the range known to be both clinically and immunologically effective.¹⁰ However, immunotherapy continues to show further symptom improvement with time and total cumulative antigen dose. At 2 years into immunotherapy, when these patients were evaluated, they had not yet reached their maximum potential improvement, so that some trend of greater efficacy at higher doses could be anticipated. Also as expected, there was a highly significant ($P = 0.0001$) relationship between degree of symptom improvement and duration of immunotherapy. In fact, we found that most patients with poor responses to immunotherapy stopped their treatment within 1.5 years. A significant therapeutic response to immunotherapy was observed in most patients who received immunotherapy for at least 2 years or more, thus we agree with Ohashi et al,¹⁶ that at least this duration of treatment is essential to immunotherapy efficacy.

In a pilot study of mite immunotherapy on allergic rhinitis patients, Ewan et al¹⁸ showed both reduced nasal symptoms and increased resistance to nasal challenge after 3 months of immunotherapy. Subsequently, their group showed efficacy of mite immunotherapy in 20 patients, with both decreased symptoms and increased resistance to conjunctival challenge, but these patients had 13 systemic reactions, a rate per injection of 2.5%.¹⁹ Ohashi et al²⁰ also found a significant 0.12% systemic reaction rate per injection in 386 patients treated for up to 5 years with mite immunotherapy. Since the technique of allergen immunotherapy was introduced in early twentieth century, anaphylaxis has always been the major risk. Besredka and Steinhart²¹ concluded that the problem was not that immunotherapy was inherently dangerous, but rather, immunizing too rapidly or with too large a dose of allergen was risky. Therefore, strict attention must be paid to

risk factors and management techniques to minimize serious reactions.^{7,10,11,20}

In this study, by use of RAST testing, a moderate escalation schedule, and an optimum maintenance treatment dose, injection site large local reactions occurred in less than 5% of patients. True systemic reactions to immunotherapy were very rare, occurring in only 5 (1%) of patients, during a mean immunotherapy treatment course of 2.5 years. All reactions were successfully treated in the office, and all patients continued with therapy following dose adjustment. The risk of systemic reaction per injection was calculated to be 0.008%, essentially identical to the rate reported for immunotherapy based on intradermal dilutional skin testing, another quantitative testing method.¹¹ The very low frequency of systemic reactions observed in the current study is likely a result of 4 factors. First is the use of RAST testing, which utilizes the mR class to independently select a safe and effective initial immunotherapy dose for each antigen. This minimizes reactions due to beginning immunotherapy at an excessively high dose. Second, a moderate dose escalation schedule was used, so that even co-seasonal antigen administration was gradual enough to minimize the risk of exacerbating existing allergy symptoms. Third, RAST testing also identifies when allergens differ greatly in their degree of sensitivity, so that these can be treated with different allergen doses in the preparation of immunotherapy treatment vials.²² Less sensitive allergens are dosed at a high antigen concentration, whereas highly sensitive allergens are given at a dilute concentration, and this ability to tailor the antigen mix for multi-antigen treatment vials helps to reduce reactions caused by unanticipated high sensitivity antigens. Finally, use of the optimum dose, rather than the maximum tolerated dose, for maintenance immunotherapy significantly reduces the risk of maintenance dose reactions, since there is less chance of fluctuating environmental antigen levels adding to the slightly lower immunotherapy dose to exceed the symptom-producing threshold.

CONCLUSIONS

This large prospective clinical study of modified RAST-based immunotherapy demonstrates both an excellent safety profile and good clinical efficacy in patients with perennial allergic rhinitis with or without asthma. Use of a quantitative testing technique can be helpful to clinicians and patients by predicting the potential for strong reactions to immunotherapy, and by allowing individualized treatment doses tailored to each patient's specific levels of allergen sensitivities. The result is an effective and safe immunotherapy treatment program.

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