

Immunotherapy: A one-year prospective study to evaluate risk factors of systemic reactions

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Background: We did a prospective study in Atlanta, Georgia, during 1991 on the rate of systemic reactions caused by immunotherapy in a clinic that uses aqueous allergen extracts.

Methods: Immunotherapy reactions were monitored. Symptoms were recorded with respect to time of onset, involvement of respiratory tract or skin, and presence of hypotension.

Results: There were 98 systemic reactions in 96 patients (1 per 1600 visits or 1 per 47 patients). There was no direct relationship to seasonal pollen counts. There was, however, a correlation with the August to October increase in mold counts. There was no correlation between reactions and the age of the patient or the age of the extract. Patients were more likely to experience a reaction during the buildup phase than during maintenance therapy. The time of onset and the severity of the reaction were in agreement with previous reports. Severe reactions that included hypotension all occurred less than 30 minutes after the injection. In contrast to previous reports, patients with asthma were not at higher risk for a systemic reaction.

Conclusion: Immunotherapy has a significant but low rate of systemic reaction. Potentially serious reactions may be mitigated by taking extra precautions during the earlier phases of an immunotherapy program and during seasons when mold counts are high. (*J ALLERGY CLIN IMMUNOL* 1995;95:8-14.)

Key words: Immunotherapy, systemic reaction, hypotension, mold counts, build-up

Since the introduction of immunotherapy^{1,2} for the treatment of allergic disorders, this form of therapy has been widely used by physicians. Despite over 80 years of experience with this mode of therapy, the medical literature is divided as to its use in allergic disease.³⁻⁷ Immunotherapy is a potentially dangerous therapy, with a small but definite potential for fatal reactions.⁸ There are several reports in the literature that attempt to identify patients who are candidates for this therapy and those who are at risk for developing a systemic reaction.⁹⁻¹¹ There is an increased risk of systemic reactions, which has been documented to be most likely associated with: (1) increasing the dose of extract during the buildup period, (2)

changing extracts, (3) patients who have experienced prior systemic reactions, (4) highly allergic (sensitive) patients; (5) patients receiving β -adrenergic blocking agents, and (6) allergen exposure during the relevant pollen season.¹²

This study attempted to prospectively examine the use of immunotherapy in a large urban allergy practice to determine whether there are other factors present in the patient, the environment, or the treatment that would predict the risk of systemic reactions. It was not our intention to evaluate the reason or the outcome of immunotherapy, but rather to assess the risk.

METHODS

This study was carried out prospectively during 1991 in the offices of the Atlanta Allergy Clinic. It included all patients to whom allergy injections were given in the office during that year. They were evaluated by skin prick and intradermal testing with individual pollens, household inhalants, and molds. No mixes were used. After their allergy injections, patients were asked to wait in the office for a minimum of 20 minutes and to report any

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symptoms that they may have experienced. If they reported no symptoms within 20 minutes, they were allowed to leave the office and were asked to call or return should any symptoms occur later. It is possible that reactions did occur but were not reported and were treated either at home or at another medical facility. Patients were questioned before each injection regarding any problems that occurred after their last injections.

When patients reported symptoms after injections, they were appropriately treated, and data were collected with respect to the time of onset, involvement of the respiratory tract or skin, and the presence of hypotension. Subsequently, data were obtained regarding pollen and mold counts, age of the extract, antigens to which the patient was found to be allergic, degree of skin test positivity, and basic demographic information. Data collection was completed on December 31, 1991.

A random sampling of typical patients receiving allergy immunotherapy at the Atlanta Allergy Clinic was performed. This consisted of a chart review of 100 consecutive patients who received allergy injections in the spring of 1992. They represent a significant sample of individuals receiving injections. Comparisons were made between this group and a group of patients who experienced systemic reactions to determine whether risk factors that predispose a patient to a systemic reaction existed. The data from this group can be found in the accompanying tables and text, and this group will serve as a comparative group with presumably the same chance of experiencing a systemic reaction from receiving allergy injections.

Pollen and mold counts, obtained by rotorod sampling, were determined 5 days a week, except during the peak of the spring and fall pollen seasons, when they were determined daily. They were performed in the offices of the Atlanta Allergy Clinic, which is certified by the Academy of Allergy and Immunology as a regional pollen and mold counting center.

Statistical analysis

The monthly injection reaction data were compared with the mean monthly pollen and mold counts by means of multiple regression analysis. The data were also subjected to a power analysis with Pearson's correlation coefficient.

RESULTS

There were 162,436 injection visits (a visit constitutes one patient receiving one or more allergy injections on a single day) totaling 346,251 individual injections, which were given to 4578 patients. These were administered by nurses specifically trained in allergy, the administration of allergy extract, and the recognition and treatment of allergic reactions. They were prescribed by nine different physicians and administered in nine different offices.

TABLE I. Analysis of rates of systemic reactions in patients in buildup and maintenance phases of immunotherapy

	Buildup	Maintenance	<i>p</i> Value
Patients	1,887	2,691	—
Visits	38,287	113,550	—
No. of systemic reactions	36	62	—
Rate/Patients	1/32	1/47	NS
Rate/Visit	1/1063	1/1831	0.01

NS, Not significant.

All injection visits were analyzed by frequency of administration of the injections and concentration of the material given with respect to whether the patients had reached the full concentration. There were 38,287 injection visits by 1887 patients in whom the extract concentration was in varying stages of "building up" to the full concentration. Injections were given twice weekly in the majority of individuals, but the interval may have been longer in some for a variety of reasons. There were 36 systemic allergic reactions in this group, representing a per patient rate of 1 in 52 and a per injection rate of 1 in 1063.

Once the patients reached their full or "maintenance" concentration of 1:10 per antigen (1:100 per aggregate in a vial), the frequency of injections gradually diminished until the patients received their ongoing maintenance therapy in one injection per month.

One thousand eight hundred fifty-eight patients received injections weekly for a total of 96,616 injection visits (Table I). Four hundred forty-nine patients received injections every 2 weeks (11,624 injection visits), 117 received injections every 3 weeks (2106 injection visits), and 267 received injections monthly (3204 injection visits). The number of individuals receiving injections at full concentration was 2691 for a total of 113,550 injection visits. Sixty-two systemic allergic reactions occurred after injections in this group, representing a per patient rate of 1 in 47 and a per injection rate of 1 in 1831. The difference between per injection rate between the full concentration and the buildup was significant ($p = 0.01$). Because of the small number of reactions occurring at each age, analysis of reaction rates by age did not prove useful.

Ninety-eight systemic reactions occurred during the year in 96 patients (1 per 1600 visits or 1 per 47 patients). The age of the patients experiencing

TABLE II. Analysis of systemic reactions by age and diagnosis

Patient age (yr)	Number	Diagnosis	Number	Clinic control population
1-10	10	Asthma	9	12
11-20	13	Rhinitis	65	70
21-30	20	Asthma and rhinitis	22	14
31-40	25	Insect hypersensitivity	2	4
41-50	23			
>50	7			

these reactions ranged from 8 to 55 years. There were 40 male and 56 female patients. The majority of patients (63%) who receive their injections in the Atlanta Allergy Clinic are women between 20 and 40 years old (range, 2 to 67 years; mean, 31 years). The number of reactions compiled by age and sex followed the pattern of frequency of injections in the clinic (Table II). Each systemic reaction is described as an individual episode despite the fact that two individuals experienced two reactions during the year. The number of injection visits per month is shown in Fig. 1. There was no correlation between the number of injections and the monthly frequency of systemic reactions.

The mean monthly pollen counts for the Atlanta area for 1991 are shown in Fig. 2. The pollen season in Atlanta starts with tree pollen in February and peaks with the combination of tree and grass pollens in April. During the summer months the levels fall to insignificant and probably non-clinically relevant levels. There is a second pollen season, consisting of ragweed as the major pollen, which begins in mid-August and lasts to the beginning of November. The number of systemic allergic reactions per month was plotted against the monthly pollen counts (Fig. 2). There was no direct correlation between the pollen counts and the occurrence of reactions. The highest number of reactions per month did occur, however, at the beginning of the ragweed season but did not correlate directly with the pollen counts. The lowest numbers of systemic reactions occurred out of the pollen seasons (November and December).

The mean monthly mold counts for the Atlanta area for 1991 are shown in Fig. 2. With the increase in humidity, the mold counts rise during the summer months. There were two peaks during 1991. The first occurred as part of the progressive rise in

mold counts found each year during August, and the second occurred after a prolonged period of rain during the third week of September. Injection reactions per month were plotted against the mold counts (Fig. 2). There was a correlation between the number of systemic reactions and the mean monthly mold counts (Pearson's correlation coefficient = 0.6754, $p < 0.01$). There was a rise in reactions during the summer when the counts rose, and there were fewer reactions when the mold counts were lower in November and December.

The majority of patients (62 of 98) who experienced reactions were receiving the full concentration of extracted material (1:100 wt/vol). (This was no different from the age or concentration of extract in the random sampling of 100 patients receiving immunotherapy in the clinic.) Although most reactions occurred with full concentration, there were reactions experienced by patients who received much more dilute concentrations, which indicates that reactions may occur with extract of any age and any concentration.

Injections generally begin with a concentration of 1:100,000 wt/vol aqueous extract and are administered twice weekly during the buildup period until the full 1:100 wt/vol concentration is reached. The injection frequency is then reduced gradually over approximately 1 to 1½ years to monthly injections. It appears that those individuals who receive their injections either two times a week or weekly are less likely to have an injection reaction (Table III). This information is skewed because it does not reflect the concentration of extract being given in many cases. What should be noted is that there were four individuals who experienced a systemic reaction after their first injection and that injection reactions could occur at any frequency of administration and even in those individuals who were receiving their injections on a monthly basis and have been receiving injections for a long time. In the random sampling of 100 patients receiving injections, 21 were receiving their injections on a monthly basis. On the other hand, only 4% of the systemic reactions described were in the patients receiving monthly injections. Therefore lengthening the interval from 2 weeks to 4 weeks did not increase the likelihood of a systemic reaction.

The patients experiencing reactions were sorted with respect to allergic diagnosis. Of the 98 reactions, the diagnosis of asthma alone was given 9 times, rhinitis alone 65 times, and both asthma and rhinitis 22 times; there were two systemic reactions in patients with insect hypersensitivity (Table II). These patterns of reactions correlate to the ratio of

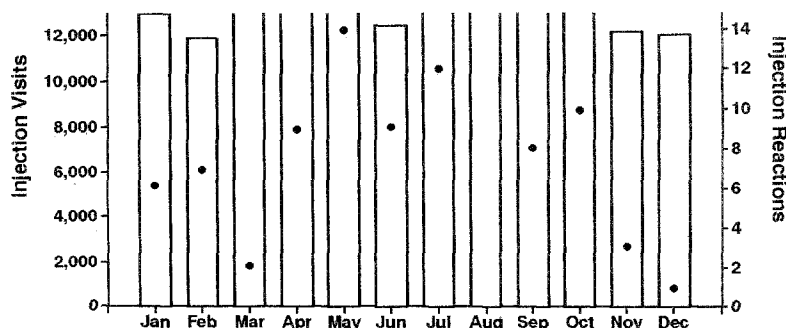


FIG. 1. Injections given and occurrence of systemic reactions by month for 1991.

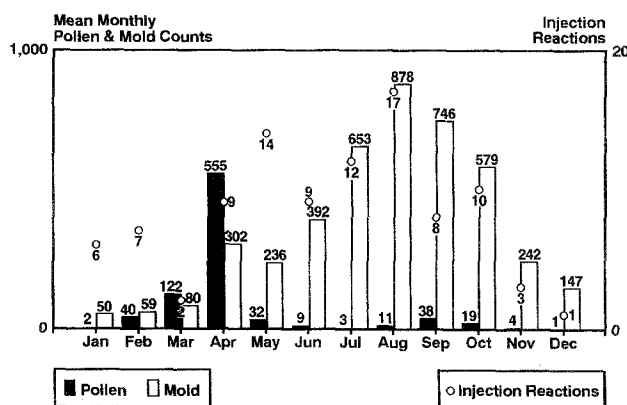


FIG. 2. Comparison of monthly occurrence of pollen and mold counts and number of systemic reactions.

diagnoses found in the clinic as a whole. This represents a risk rate of experiencing a reaction by diagnosis in this population of 1 in 57 patients with asthma and 1 in 41 patients with allergic rhinitis ($p > 0.05$).

Skin test responses are shown in Table IV. Skin prick tests were performed initially in all patients with 1:20 wt/vol concentration of extract material. If these tests failed to demonstrate a positive reaction, the material was applied again intradermally with a 1:1000 concentration. Three patients had previously been transferred from another physician to our clinic, and no record as to the testing technique used was reported. Two patients were diagnosed as having insect hypersensitivity, and no inhalant skin tests were performed. In the group for which data were available, 93 patients were found to be allergic to the dust mite. Sixty-seven had positive responses to prick test, and 26 had positive responses to intradermal test. (Ninety-eight of 100 random clinic patients had positive

TABLE III. Analysis of systemic reactions by frequency of administration

	No. of reactions	Rate by injection visits	Clinic control population
First injection	4		—
Twice a week	21		24
Weekly	41	1/2356	30
Every 2 weeks	23	1/505	17
Every 3 weeks	4	1/526	8
Every 4 weeks	4	1/801	21

mite skin test responses, 70 by prick test and 28 by intradermal test.) Ninety-two patients were found to be allergic to pollens. The prick test results were positive in 67 patients, and intradermal test results were positive in the remaining 25 patients. (In the random clinic population in which 98 of 100 patients had positive reactions to pollens, 68 had positive reactions to prick tests and 30 had positive

TABLE IV. Comparison of the rates of systemic reactions by sensitivity to mites, pollens, and molds

	Mite				Pollen				Mold			
	Reaction		Clinic		Reaction		Clinic		Reaction		Clinic	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
% Puncture	67	72	70	71.4*	67	72	68	69*	48	51	32	35†
Intradermal	26	27.9	28	28.5*	25	27	30	30.6*	42	41	59	64.4†
Not tested or reactive	—	5	—	2	—	7	—	2	—	9	—	9

Clinic refers to control group.

*Not significant.

† $p = 0.01$.**TABLE V.** Analysis of severity of systemic reaction by time of onset

Minutes	No.	Type of reaction		
		Respiratory	Skin	Hypotension
0-10	25	20	22	3
11-20	32	26	24	3
21-30	13	9	8	1
31-40	7	4	4	0
41-50	4	3	3	0
51-60	6	4	6	0
>60	11	6	8	0
Total	98	72	75	7

Note: Patients may experience more than one type of reaction

reactions to intradermal tests.) Mold tests elicited positive reactions in 90 patients, 48 by prick test and 42 by intradermal test. In the random sample of 100 patients, 91 had positive reactions. However, only 32 prick test results and 59 intradermal test results were positive. A comparison of skin test reactivity to mold in patients experiencing systemic reactions and in the general clinic population was made. The results indicate that individuals experiencing a systemic reaction were significantly more sensitive to molds as determined by skin testing than those in the general clinic population ($p = 0.010$). It should also be noted that the pattern of appearance of systemic injection reactions during the course of the year was similar to the level of mold counts measured in the Atlanta area during the course of that year (Fig. 2).

The reactions experienced by the patients were separated into categories according to the time the reaction was first noticed (Table V). Twenty-five

patients had reactions within the first 10 minutes. Of these, 20 patients experienced respiratory symptoms (listed as "difficulty breathing" or "wheezing" on the injection reaction form), 22 had hives, and 3 had hypotension. Of 32 patients who had onset between 11 and 20 minutes, 26 had respiratory symptoms, 24 had hives, and 3 had hypotension. Of 13 patients who had onset between 21 and 30 minutes, 9 had respiratory symptoms, 8 had hives, and 1 had hypotension. There were seven severe reactions involving significant hypotension. These occurred in less than 30 minutes, with six occurring in the first 20 minutes. Five severe reactions were also associated with respiratory distress. There were 28 patients who had the onset of their symptoms more than 30 minutes after their injections (29%). These reactions included an almost equal distribution of respiratory and dermal reactions, but none with hypotension. Only one person, a patient with asthma, demonstrated dyspnea as a manifestation of the systemic reaction, and two others had wheezing as part of the reaction when it began 30 minutes or more after the injection.

DISCUSSION

The safety of immunotherapy for allergic disorders has been the topic of study, editorials, treatises, and government policy almost since its first description in 1911. Although there have been reports of deaths among patients who have received this form of therapy, it is generally considered a rare event and in most cases avoidable. Nonfatal generalized reactions are far more frequent, although the rate is low when treatment is administered by properly trained individuals in a medically equipped facility. The number of systemic reactions that could result in death if im-

properly monitored and treated cannot be estimated. All systemic reactions should be considered potentially life-threatening. This concept has led to guidelines and restrictions that have been published by the World Health Organization, the International Union of Immunological Societies,⁹ and the United Kingdom's Committee on Safety of Medications.¹¹ This study prospectively examined an urban population of children and adults who were receiving allergy immunotherapy to determine the frequency of systemic reactions and whether there were any factors that might alert the physician to a high-risk situation.

Several articles report frequency rates for systemic allergic reactions.^{10, 13} Our patients demonstrated a rate of 1 in 1600 allergy injection visits in 1 of 46 patients. This does not include patients who experienced a reaction outside of the office after the initial 20 minutes of observation and did not report the occurrence when they returned for the next visit or injection. This presumably is a small number. This rate is less than the rates quoted for rush immunotherapy with pollens¹⁴ but is not much different from rates reported for standard treatment regimens.

The purpose of this study was to identify factors that might alert the physician to increased risk for systemic reactions. There was no distinct relationship between age and reaction rate. Reactions did not correlate with the pollen seasons. Rate increased in August, which may reflect the beginning, but certainly not the peak, of the ragweed pollen season in Atlanta. More reactions occurred when the pollen counts were relatively low. However, there was a correlation between reaction rate and mold counts. Mold counts increased during the summer and early fall months, which coincided with an increase in systemic reaction rate. Prick test positivity to molds was more frequent in patients who had reactions than in patients who did not have reactions ($p = 0.01$). The correlation with mold counts might indicate a risk factor for systemic reactions. A previous study indicated more frequent asthma attacks at times when the mold counts have been elevated.¹⁵ Further investigation of the relationship of mold sensitivity, mold spore counts, and the risk for a systemic reaction with immunotherapy seems to be indicated.

There was no correlation between the age of the extract and the rate of systemic reactions. Reactions were more likely to occur during the buildup period than during maintenance therapy at full concentration (1 in 1063 injection visits vs 1 in 1831

injection visits). Four patients had reactions at the first dose of the weakest concentration; on the other hand, four patients had reactions after they had been receiving their injections for longer than 2 years and were receiving the full concentration of extract at monthly intervals. It appears that a reaction is possible at any time and at any concentration during a treatment program, even though the risk is higher during the early phases of therapy when lower concentrations of allergen extract are used.

There was no distinct increase in the rate or severity of reactions in patients with asthma. This is somewhat different from rates in previous reports.^{9, 14} There were 18 patients whose only complaint and finding was respiratory difficulty among the 72 patients who reported respiratory complaints. This was not limited to individuals with the diagnosis of asthma. All seven patients with severe hypotension reported respiratory difficulty. Some asthmatic patients experienced urticaria as their only symptom. There is no explanation for the difference in this study compared with other reports in which the incidence of death appeared to be correlated with the diagnosis of asthma in those with systemic reactions.

The time of onset and the severity of the reaction are in agreement with previous reports. Seven patients demonstrated significant hypotension. All of the more severe reactions occurred within 30 minutes after the injection and were treated promptly to resolve the reaction. Twenty-eight reactions began at least 30 minutes after the injection administration. This is also in keeping with previous reports.^{15, 16} Although a systemic reaction after a patient has left our facility is a cause for concern, it is somewhat reassuring to note that none were severe with hypotension. The current recommendation of the World Health Organization to monitor a patient for 30 minutes after an allergy injection seems appropriate, but some systemic reactions will occur later.

The decision to start an individual on allergy immunotherapy should not be taken lightly. Risks might be mitigated by taking precautions during the earlier stages of the injection program and during the peak of pollen or mold seasons. These precautions may include a slower buildup of antigen or a reduction of dose during peak seasons. Patients should receive their injections in a medically equipped facility from properly trained individuals and should be monitored for a minimum of 30 minutes after the injections.

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