

Skin Testing at the Cessation of Immunotherapy

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ABSTRACT

The value of repeat skin testing at the time of cessation of immunotherapy was examined in 37 of 66 children treated for inhalant allergies. Results after 2 years indicated no difference in outcome between the group tested and given specific environmental avoidance recommendations based on results versus those not tested. Further, results were not predictive of eventual outcome.

INTRODUCTION

IMMUNOTHERAPY HAS BEEN RECOGNIZED as an adjunctive tool of the allergist in the management of patients with allergic disorders.⁽¹⁾ Unfortunately, clinical practitioners have no definitive test available to determine the ideal time for immunotherapy cessation in the patient who has achieved some benefit. At present, the usual recommended length of treatment is 3–5 years.^(1,2)

The value of repeat skin testing, however common among practitioners, is not clear. There are several considerations in this regard. First, the procedural technique and the extract potency may not be identical at the time of initial and repeat testing, making comparisons difficult. Second, clinical improvement may result from alterations in the immune response that are not totally reflected by the skin test results.⁽³⁾

A review of the literature indicates that 11 studies examined skin test reactions during immunotherapy^(4–14) (mostly pollen), and all but 1⁽⁶⁾ reported decreased reactivity. Six of the studies^(9–14) attempted to correlate the skin test results with the clinical response to immunotherapy. Although in general, there was a trend toward decreased skin reactivity with clinical improvement, tests rarely became negative, and exceptions commonly occurred. Clinical experience has certainly confirmed the lack of a direct correspondence between the size of a skin test reaction and the severity of symptoms or clinical response.⁽¹³⁾

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Therefore, skin tests appear to be only a crude index of the degree of clinical sensitiveness,⁽¹⁵⁾ and one wonders if they should serve as a guide for management when contemplating cessation of immunotherapy. For example, continued environmental precautions might be warranted in an individual with persisting positive skin tests despite a good clinical response. Skin testing might allow the clinician to identify any new allergies that could conceivably cause problems and prophylactically institute early environmental control measures.

In previous studies where decreased skin reactivity was noted, long-term follow-up was not provided to determine if the clinical improvement was sustained. Data regarding patient outcome several years after the cessation of immunotherapy and the relationship of skin testing and clinical response are not found in the literature. Hence, this study was undertaken to determine if skin testing at the time of immunotherapy cessation is of value.

METHODS

The charts of all children who had previously received immunotherapy for inhalant allergies were retrospectively reviewed (pollen, mold, dust, mite). Any child who was not subsequently followed over a minimum of 2 years was omitted from the study. Reasons for initiating immunotherapy consisted of a failure to adequately control symptomatology through environmental manipulation and medication use over a period of 1 year observation (85%), intolerance of medication (10%), and poor compliance (5%). Immunotherapy was between 2000 and 4000 protein nitrogen units (PNU)/ml of each allergen, as tolerated.

All patients were followed up by this investigator at each visit. The factors noted were initial diagnosis, age of the child, duration of immunotherapy and antigens used, pattern of symptomatology (perennial vs seasonal), and duration of follow-up. The degree of symptoms and the need for medication were recorded. Patients were divided into two groups: Group A had skin tests preimmunotherapy and postimmunotherapy (at parent's request), whereas Group B had initial skin tests only. Environmental control was ordered for the remaining positive tests postimmunotherapy.

The first consideration was the eventual outcome after the cessation of immunotherapy. The final 2 years while receiving immunotherapy were used for comparison with the postimmunotherapy period, constituting at least the first 2 years not receiving injections. Two subgroups were formed: Group 1 with no significant increase in symptomatology and Group 2 who demonstrated a subsequent significant increase.

Criteria were established to determine what constituted a significant increase in symptomatology (Table 1). A score difference between study intervals > 3 was considered significant.

After classifying the children according to eventual outcome, skin testing results were examined to determine if they had any value in predicting the possible redevelopment of symptomatology after completion of immunotherapy.

Skin testing procedure consisted of first applying prick tests (Hollister-Stier aqueous extracts). A 2+ test was erythema larger than 2cm with a wheel of 5mm. If $< 2+$ (negative), intracutaneous tests were applied up to a strength of 1000 PNU. The same observer (DS), same techniques, same grading system (standardized),⁽¹⁵⁾ same antigen strengths, and same controls were used. The tests were also generally applied at the same time of year (90% done in the same month). Preimmunotherapy and postimmunotherapy skin tests were compared noting (A) conversions of positive to negative, (B) conversions of negative to positive, and (C) persistent positive reactions with (1) decreased reactivity, (2) no change in reactivity, and (3) increased reactivity. Persistent negative reactions also were recorded. The criteria for skin test comparisons are noted in Table 2.

RESULTS

There were 75 children who had been receiving immunotherapy whose charts were reviewed, and 66 children fulfilled the criteria of a minimal 2-year postimmunotherapy observation period.

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TABLE 1. SCORING SYSTEM TO COMPARE DEGREE OF SYMPTOMATOLOGY AND MEDICATION USE

Classification of symptoms

Mild: Any two rhinitis or conjunctival symptoms (sneezing, nasal stuffiness, or rhinorrhea, conjunctival itching or nasal itching, eye angioedema, conjunctival injection), hacky cough or wheeze with prolonged exercise (5 min) that resolves spontaneously

Moderate: Between three and five of the mild symptoms or wheezing with exertion, wheezing at night, or paroxysmal coughing

Severe: > five of the mild symptoms or wheezing at rest.

Scoring system: Points

0, no symptoms or medication use

1, mild symptoms

3, moderate symptoms

5, severe symptoms, if present 50% of the time, add 1 point

Medication use

1, nasal or eye symptoms requiring antihistamines

3, asthma requiring bronchodilators

Add 1 point if used 25–50% of the time

Add 2 points if used > 50% of the time or daily topical cromolyn

Add 3 points for use of topical or oral steroids

TABLE 2. CRITERIA FOR SKIN TEST COMPARISONS

Conversion of negative to positive

Initial skin test	Follow-up skin test
< 2+ at 1000 PNU	Positive prick ($\geq 2+$)
	IC ^a 100 PNU $\geq 2+$
	IC 1000 PNU = 3–4+

Conversion of positive to negative

Initial skin test	Follow-up skin test
Prick = 2–4=	Negative prick and
	IC 1000 PNU < 2+
IC 100 PNU = 2–4+	I.C. 1000 PNU < 2+

Significant change in reactivity

1. Over a 2-stage variation within the same dilution (e.g., 1+ $\rightarrow$ 4+)
 2. Over a 1-stage variation using the next strength dilution or IC to prick (e.g., 100 PNU = 4+ $\rightarrow$ 1000 PNU = 2+)
-

^aIC, intracutaneous.

Six children had been not receiving immunotherapy only 18 months, and another 3 children moved away from our area and were lost to follow-up. Of the 66 children, repeat skin testing was done in 37 (Group A), whereas 29 had no repeat testing (Group B). The boy/girl ratio was similar in both groups. Age range at the start of immunotherapy was 3 to 14 years in both

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TABLE 3. GENERAL GROUP COMPARISONS

	<i>No. of patients</i>	<i>Boy/girl</i>	<i>Mean age (years)</i>	<i>Mean IT^a (years)</i>	<i>Mean Obs^a (years)</i>	<i>Diagnosis</i>		
						<i>AR^a</i>	<i>As^a</i>	<i>AR + As</i>
Group A	37	30/7	8.5	4.5	2.5	30%	21%	49%
Group B	29	20/9	8.3	4.2	2.9	21%	31%	48%

^aAR, allergic rhinitis; As, asthma; It, immunotherapy duration; obs, observation interval post immunotherapy.

TABLE 4. EVENTUAL OUTCOME RESULTS BY DIAGNOSIS

	<i>Total</i>	<i>Rhinitis</i>	<i>Asthma</i>	<i>Rhinitis + Asthma</i>
Group A1	24 (65%)	8 (73%)	7 (88%)	9 (50%)
Group A2	13 (35%)	3 (27%)	1 (12%)	9 (50%)
Group B1	19 (66%)	6 (100%)	6 (67%)	7 (50%)
Group B2	10 (34%)	—	3 (33%)	7 (50%)

TABLE 5. SYMPTOM SCORES (SS) AND SKIN TEST (ST) RESULTS

	<i>Mean SS/Child^(a)</i>		<i>Mean No. + ST/Child^(b)</i>	
	<i>Pre^(c)</i>	<i>Post^(d)</i>	<i>Pre</i>	<i>Post</i>
Group A1	5.0	4.5	5.7	4.0
Group A2	4.0	7.4	6.6	3.7
Group B1	4.9	3.2	7.7	-
Group B2	4.9	7.5	5.1	-

^aIn relation to cessation of immunotherapy.

^bIn relation to immunotherapy course.

^cPre, before cessation of immunotherapy.

^dPost, after cessation of immunotherapy.

groups, with a mean of 8.5 years in Group A and 8.3 years in Group B. The mean duration of immunotherapy and length of observation after cessation were similar in both groups. The variety of initial diagnosis was similar also in both groups (Table 3).

The clinical outcome of both groups was examined, with two thirds of each group showing no increase in symptoms after cessation.

There was no significant difference in groups with the outcome as noted by diagnosis. Fifty percent of the patients with rhinitis and asthma in combination did poorly. The majority of children with allergic rhinitis or asthma appeared to have no further worsening of their condition (Table 4).

In examining the baseline symptom scores (mean value), there was no significant difference between the children who had no increase in symptoms (Group 1) versus those who did worsen (Group 2). In both the groups who worsened, there was a 50–85% increase in symptom score values compared to a slight decrease in those who did well. The number of mean positive skin tests per child preimmunotherapy did not differ in either group, and there was a decrease in the mean number of positive tests noted postimmunotherapy in both the group who did well and the group who had an increase in symptoms (Table 5).

One might also note from these observations that environmental control, which was ordered on all patients with positive skin test results (Group A), had no apparent effect on outcome, since there was no difference in the proportion of patients in Group A or Group B who did well.

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TABLE 6. DIMINISHED SKIN TEST REACTIVITY BY ANTIGENS

	<i>Group A1^a</i> (%)	<i>Group A2</i> (%)
Dust	55	50
Tree	36	40
Grass	35	73
Ragweed	40	77
Molds	61	27

^aGroup A1 had 75% of patients still allergic to molds on skin testing (development of new allergy).

In examining skin test reactivity results, we note that in Group A1 (those who did well postimmunotherapy), 12% reverted to negative skin tests, 25% continued with previously positive tests, and 63% had new positive tests in addition to the previous tests remaining positive to some degree. In the group (A2) that did less well after immunotherapy cessation, 8% reverted to negative tests, 46% still had previous tests remaining positive, and 46% had new positive tests in addition to the old ones. Hence, skin testing results did not appear to reflect a better outcome.

In examining the results of individual antigen reactivity between the two groups (Table 6), we note that the group with a better outcome (Group A1) had less of a decrease in pollen skin test reactivity than did the group that subsequently had increased symptoms (Group A2). One wonders if the results may have misled the patients into a false sense of security, resulting in more laxity in pollen avoidance measures. However, in the group who had no skin testing performed, the same proportion of patients developed increased symptoms. It is interesting that there was a larger proportion of decreased mold reactivity in the group who remained improved, although 75% of this group still had positive mold tests in view of the development of more new allergies.

DISCUSSION

A review of 66 children who received immunotherapy for inhalant allergies failed to demonstrate any benefit from skin testing performed at the time of immunotherapy cessation. There was no significant difference in the eventual outcome of those children who had skin testing with environmental avoidance measures recommended based on results versus those who did not receive it. Skin test results also were not predictive of final outcome.

One wonders if bias occurred, since patients who requested repeat skin testing (Group A) might reflect greater anxiety about their condition and would complain more frequently. However, the majority of those desiring skin testing noted no further exacerbation of their symptoms after immunotherapy cessation. One would expect to see a high total mean symptom score for Group A compared to Group B, and this was not observed. Further, one could also expect these people to more strictly enforce environmental control measures that could result in lower symptom scores; however, this was not observed.

In reviewing reasons that parents used for not desiring repeat skin tests we found (1) the fact that our present state of knowledge could not prove it would be useful and (2) the desire to avoid a potentially uncomfortable procedure on their child.

A review of other factors that could potentially influence results (i.e., asthma scores) included incidence of viral illness, exercise patterns, and compliance with medications; however, these appeared to be constant factors for all groups during the observation period after immunotherapy cessation.

The results of this study are not surprising in view of several known facts. Extract potency may vary considerably from lot to lot, since methods of standardization are not yet ideal,⁽¹⁶⁾ making comparisons of skin testing results difficult. The stability of extracts also represents a potential problem affecting potency at any given time. As mentioned, most previous studies⁽⁴⁻¹⁴⁾ did indicate

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a general trend toward decreased skin reactivity during immunotherapy, and this correlated frequently with clinical improvement. However, tests rarely became negative.⁽¹³⁾ This was noted also for the children reported in this study. Exceptions to the trend have been reported commonly, and again, this study confirms those findings. It is known that immunotherapy results in definite immunological changes,⁽³⁾ including (1) a gradual decline in serum-specific IgE, (2) an increase in serum-specific IgG (blocking antibody), and (3) decreased basophil reactivity and sensitivity to specific antigens. Since multiple factors appear to influence the severity of symptoms, it would be surprising to discover that one of them alone correlates highly with the degree of clinical improvement, and decreased target organ sensitivity to provocation challenge (nasal or bronchial) with specific antigen has been demonstrated. However, they show no consistent correlation with the immunological and physiological changes.

Therefore, one might expect the results observed in this study. There appears to be no predictive value for performing skin testing at the end of immunotherapy. Yet it appears to be a common clinical practice. An argument could be made that it would be of benefit in recommending environmental precaution measures based on positive results. However, such measures were followed in this study, and there was no apparent effect on outcome. In conclusion, skin testing at the end of immunotherapy appears unwarranted. A prospective study would be ideal and would more precisely determine its value to the clinician.

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