

A CONTROLLED TRIAL OF IMMUNOTHERAPY FOR ASTHMA IN ALLERGIC CHILDREN

N. FRANKLIN ADKINSON, JR., M.D., PEYTON A. EGGLESTON, M.D., DONALD ENEY, M.D., EUGENE O. GOLDSTEIN, M.D., KENNETH C. SCHUBERTH, M.D., JOHN R. BACON, M.D., ROBERT G. HAMILTON, PH.D., MICHAEL E. WEISS, M.D., HASAN ARSHAD, M.D., CURTIS L. MEINERT, PH.D., JAMES TONASCIA, PH.D., AND BARBARA WHEELER, R.N., B.S.N.

ABSTRACT

Background Injections of allergens are widely prescribed for patients with asthma, but little is known about the effectiveness of immunotherapy.

Methods We conducted a double-blind, placebo-controlled trial of multiple-allergen immunotherapy in 121 allergic children with moderate-to-severe, perennial (year-round) asthma. The children, who required daily medication for their asthma, were randomly assigned to receive subcutaneous injections of either a mixture of up to seven aeroallergen extracts or a placebo. Maintenance injections were continued for 18 months or longer. Medications were adjusted every two to three weeks on the basis of peak flow rates and symptoms. The principal outcome was the daily medication score. Bronchial sensitivity to methacholine (the concentration provoking a 20 percent decrease in the forced expiratory volume in one second [PC₂₀]) was measured twice yearly.

Results The median medication score declined from 5.4 to 4.9 in the immunotherapy group ($P < 0.001$) and from 5.2 to 5.0 in the placebo group ($P < 0.001$), but there was no significant difference between the groups ($P > 0.6$). The number of days on which oral corticosteroids were used was similar in the two groups. Partial or complete remission of asthma occurred in 31 percent of the immunotherapy group and in 28 percent of the placebo group ($P > 0.5$). There was no difference between the groups in the use of medical care, symptoms, or peak flow rates. The median PC₂₀ increased significantly in both groups, but again with no difference between the two groups.

Conclusions Immunotherapy with injections of allergens for over two years was of no discernible benefit in allergic children with perennial asthma who were receiving appropriate medical treatment. (N Engl J Med 1997;336:324-31.)

©1997, Massachusetts Medical Society.

INJECTIONS of aeroallergen extracts were first evaluated for the treatment of seasonal pollinosis in 1911 and have been widely used ever since as a treatment for respiratory allergy.^{1,2} Controlled trials have shown that immunotherapy relieves the symptoms of allergic rhinoconjunctivitis with minimal side effects, provided that high-quality extracts are used in sufficiently large doses.^{3,4} Studies of single-allergen models of allergic asthma have also shown that immunotherapy reduces airway sensitivity to allergens, decreases signs and symptoms provoked by natural exposure, and in some cases improves basal

airway function.^{5,6} Because there have been few clinical trials of multiple-allergen treatment for perennial (year-round) allergic asthma and they have not been well designed, we performed a randomized, placebo-controlled study of 121 children with sensitivities to multiple allergens and moderate-to-severe, perennial asthma. The purpose was to evaluate the additive benefit of broad-spectrum immunotherapy in children receiving satisfactory medical care, including currently accepted pharmacotherapy for asthma.

METHODS

Patients

We recruited 350 children from the private practices of participating physicians, from clinics, and by advertisement. All the children went through an initial period of observation and stabilization for a mean (\pm SD) of 408 ± 210 days. The children were instructed in how to manage their asthma, evaluated for compliance, and given skin-prick and radioallergosorbent tests. Their medications were adjusted with the use of an algorithm every two to three weeks to maintain optimal therapy. We visited each child's home to instruct the family, evaluate the home environment, and sample house dust. Children whose parents were unwilling to part with furred pets were excluded from the study.

Children of either sex who were 5 to 12 years old were eligible for enrollment if they had had asthma for more than one year and had used asthma medications daily or bronchodilators five to seven days per week (including prophylactic and rescue use) for more than six months in the previous year, and if they had two or more positive skin tests, a total serum IgE level higher than the 95th percentile for their age, and family and personal histories of atopy. Eligible children, derived in about equal numbers from an inner-city population (largely black) and a suburban population (largely white), were randomly assigned to a treatment group after informed consent had been obtained from them and their parents.

Management of Asthma

At each visit, daily diaries with symptom scores, morning and evening peak-flow readings, and medication use were reviewed by a team of investigators who were unaware of the treatment assignments. They applied an algorithm that called for reductions in medication if during the previous 14 days symptom scores had been less than 2 on more than 10 days and 0 on more than 3 days, or the peak flow rate had been higher than 80 percent of the predicted value on more than 9 days. Physicians were permitted to override the algorithm on the basis of clinical judgment, and they did so frequently and equally in both treatment groups

From the Asthma and Allergy Center and the Department of Medicine (N.F.A., R.G.H., M.E.W., H.A., B.W.) and the Department of Pediatrics (P.A.E., D.E., E.O.G., K.C.S., J.R.B.), Johns Hopkins University School of Medicine, and the Departments of Biostatistics and Epidemiology, Johns Hopkins School of Hygiene and Public Health (C.L.M., J.T.) — both in Baltimore. Address reprint requests to Dr. Adkinson at 5501 Hopkins Bayview Cir., Baltimore, MD 21224-6801.

($P=0.63$). Asthma medications were provided gratis and adjusted in a stepwise fashion as follows: step 1, use of a bronchodilator as needed; step 2, regular use of a bronchodilator (theophylline or albuterol); step 3, regular use of two or three drugs (theophylline, albuterol, and cromolyn); step 4, the addition of beclomethasone in a metered-dose inhaler or alternate-day methylprednisolone; and step 5, the addition of oral corticosteroids (>0.5 mg per kilogram of body weight per day, with tapering). Acute exacerbations of asthma were treated as directed by the children's physicians, with tapered doses of oral methylprednisolone. Emergency room care and inpatient treatment were provided at the physicians' discretion.

Immunotherapy

Before randomization, one of us chose up to seven treatment allergens per child according to the results of skin-prick and radioallergosorbent tests, with a preference given to perennial allergens (dust mites and molds) over seasonal pollens. Treatment mixtures were prepared by combining 1.6 ml of the highest concentration available for each treatment allergen with albumin-saline diluent to a total volume of 9.6 ml per treatment vial, if fewer than seven allergens were used, or 11.2 ml, if seven allergens were used (in 30 children). Placebo consisted of caramelized saline with 10 μ g of histamine phosphate per milliliter.

Immunotherapy was administered blindly by a treatment team, which was also responsible for observation and treatment of any reactions. Treatment was initiated with 0.1 ml of a 1:1000 dilution of concentrate (or a 1:10,000 dilution in children with high skin reactivity). Injections were increased weekly to reach a target maintenance dose of 0.7 ml of concentrate; if a dose produced systemic reactions on two attempts, the next lower dose was used for maintenance therapy. Maintenance therapy was given every 2 weeks for 24 months and then every 3 weeks until the completion of the study.

Outcome Variables

The principal outcome measure was the amount of medication required to control symptoms and maintain peak flows within acceptable limits. We used a 10-point ordinal scale of daily medication use, as previously described.⁷ Briefly, a score of 0 indicated no medication; 2, two to four doses of albuterol; 6, inhaled beclomethasone or alternate-day methylprednisolone; and 10, a high dose of methylprednisolone (>1 mg per kilogram per day). A clinically important decrease in the score for daily medication use was defined as a reduction of two or more points.

On the basis of response rates from the most comparable previous study,⁸ we estimated a priori that a sample of 60 subjects per group would be required for an alpha level of 0.05 and a beta level of 0.8. Secondary outcome measures included the daily peak expiratory flow rate, asthma symptom score, number of days on which inhaled or oral corticosteroids were used, and number of contacts with health care providers.

Sensitivity to methacholine was measured before randomization and on average at six-month intervals thereafter, according to the methods of Chai et al.⁹ and Weiss et al.¹⁰ The results were expressed as the interpolated concentration of methacholine provoking a 20 percent fall in the forced expiratory volume in one second (PC_{20}). Tests were postponed for at least four weeks after respiratory infections, asthma flares, or burst corticosteroid treatment (rapid administration of corticosteroids followed by rapid tapering).

Statistical Analysis

Nonparametric statistics were used to determine P values for group comparisons for all outcome measures.¹¹ In the subgroup analysis of daily medication use, we used the rank transformation and two-way analysis of variance to determine whether the effect of immunotherapy differed among subgroups of children.¹² All P values reported are two-sided and were calculated with the use of SAS software for the signed-rank test, rank-sum test, and analysis of variance.¹³

RESULTS

Patients

A total of 121 children were enrolled in the study. Their average age at randomization was 9.2 years (range, 5.4 to 14), with 40 percent 8.5 years or younger. Seventy-nine percent were boys; 54 percent were white, and 45 percent were black. At randomization, 52 children (43 percent) were in stable condition with the use of corticosteroids: 41 required inhaled beclomethasone, 4 were receiving oral methylprednisolone, and 7 were receiving a combination of inhaled and oral corticosteroids. All remaining 69 children (57 percent) required daily cromolyn or theophylline, daily inhaled albuterol, or both. At base line, all the children had a PC_{20} value that was less than 2 mg per milliliter, and 71 percent had a value under 0.25 mg per milliliter. The base-line characteristics did not differ significantly between the two treatment groups (Table 1).

TABLE 1. BASE-LINE CHARACTERISTICS OF 121 ALLERGIC CHILDREN WITH ASTHMA RANDOMLY ASSIGNED TO RECEIVE IMMUNOTHERAPY OR PLACEBO.*

CHARACTERISTIC	IMMUNOTHERAPY (N=61)	PLACEBO (N=60)
Age		
Mean (yr)	9.3±2.1	9.2±2.3
≤8.5 yr (no. of children)	25	23
>8.5 yr (no. of children)	36	37
Sex (M/F)	49/12	46/14
Race (no. of children)		
White	31	34
Black	30	25
Other	0	1
Symptom score	0.3±0.27	0.4±0.35
PEFR (% of predicted value)	81.9±10.8	84.8±8.6
Medication score		
Mean	4.9±1.8	5.0±1.3
≤5.0	30	28
>5.0	31	32
Regular medications (no. of children)		
Theophylline	33	30
Cromolyn	12	13
Albuterol four times a day	46	42
Beclomethasone	18	23
Oral corticosteroids	7	9
Methacholine sensitivity†		
Geometric mean PC_{20}	0.24	0.26
95% CI	0.20–0.30	0.21–0.30
Mild (no. of children)	2	0
Moderate (no. of children)	16	15
Severe (no. of children)	43	45
Run-in phase (days)		
Mean	413±216	402±203
Range	89–1642	56–898

*Plus-minus values are means ±SD. PEFR denotes peak expiratory flow rate, and CI confidence interval. The daily symptom score, peak expiratory flow rate, and medication score were calculated as the mean scores over a 60-day period before randomization. None of the base-line variables differed significantly between the two groups.

†Sensitivity to methacholine was defined as the interpolated concentration of methacholine (in milligrams per milliliter) provoking a 20 percent reduction in the forced expiratory volume in one second (PC_{20}). Mild sensitivity was defined as a PC_{20} of ≥ 2 , moderate as >0.25 and <2 , and severe as ≤ 0.25 .

TABLE 2. ALLERGEN EXTRACTS USED FOR TREATMENT AND SENSITIVITY TO ALLERGENS IN THE TWO TREATMENT GROUPS.

ALLERGEN EXTRACT*	CONCENTRATE		MAINTENANCE DOSE (MAJOR ALLERGEN)	SENSITIVITY TO ALLERGEN	
	weight:volume	units/ml†		IMMUNO- THERAPY	PLACEBO
				(N = 61)	(N = 60)
			μg	% of children	
Dermatophagoides species (common dust mites)‡		10 ⁵	4.3 (Der p I) 5 (Der f I)	77	83
<i>Ambrosia elatior</i> (short ragweed)	1:10		26 (Amb a I)	77	77
Grass mix§		10 ⁵	38 (group I allergen)	62	75
<i>Alternaria alternata</i>	1:2		6 (Alt a I)	64	60
<i>Cynodon dactylon</i> (Bermuda grass)	1:10			54	58
<i>Plantago lanceolata</i> (English plantain)	1:10			51	50
<i>Quercus alba</i> (white oak)	1:10			41	30
<i>Cladosporium herbarum</i>	1:2			25	27
<i>Aspergillus fumigatus</i>	1:10			8	7

*Extracts were prepared and standardized as lyophilized aqueous extracts by ALK Laboratories, Copenhagen, Denmark, under a physician-sponsored investigational-new-drug application (no. 2212).

†The units were standardized units (SQ units) as defined by ALK Laboratories.

‡The extract was a mixture of *Dermatophagoides farinae* and *D. pteronyssinus*, in equal parts, obtained from whole-mite cultures.

§The extract was a mixture of *Phleum pratense* (timothy), *Dactylis glomerata* (orchard grass), and *Lolium perenne* (perennial ryegrass) in equal parts.

At randomization, the two groups were similar with respect to the composition of assigned allergen treatments (Table 2). The predominant sensitivity was to dermatophagoides mites (in 80 percent of the children), followed by short ragweed (in 77 percent) and a mixture of rye-group grasses (in 69 percent). The median number of extracts assigned for treatment was six (range, two to seven). Compliance with the medication regimen was ascertained at each visit on the basis of pill counts and the weight of metered-dose-inhaler canisters, which were compared with prescribed doses and doses recorded in diaries. For all prescribed doses, the compliance rate was 92.6 percent in the immunotherapy group and 93.6 percent in the placebo group.

Immunotherapy

The mean time from randomization to completion of the study or dropping out was 1005 ± 273 days (range, 49 to 1663) for the immunotherapy group and 1023 ± 159 days (range, 448 to 1449) for the placebo group ($P > 0.5$). Forty-three of the 61 children in the immunotherapy group (70 percent) and 57 of the 60 in the placebo group (95 percent) received the target maintenance dose (0.7 ml of concentrate) every 2 to 3 weeks for at least 18 months. Ten children in the immunotherapy group received a lower maximal tolerated dose for 18 months or more.

Eight children in the immunotherapy group and three in the placebo group dropped out before the

completion of the study because of a move (three children), family problems (six), or noncompliance (two). No child dropped out because of adverse experiences with treatment.

Primary Outcomes

Figure 1 shows the mean daily-medication score for each child 60 days before randomization (base line) and 60 days before completion of the study or dropping out (the last follow-up visit). The median score declined significantly from randomization to the last follow-up visit in both groups ($P < 0.001$). However, there were no significant between-group differences at base line or at the last follow-up visit. Partial remission (defined as only the use of albuterol, as needed) occurred in 15 children in the immunotherapy group (28.3 percent of those who completed the study) and 12 in the placebo group (21.1 percent of those who completed the study) ($P = 0.51$). An additional four children in the immunotherapy group (7.5 percent) and five in the placebo group (8.8 percent) had a complete remission (defined as no use of medication) at the conclusion of the study.

To determine whether there were treatment-related changes in daily medication use, we compared the mean change in medication scores between base line and the last follow-up visit. The magnitude of the change was similar in the two groups (mean difference, 0.22; $P = 0.37$) (Table 3).

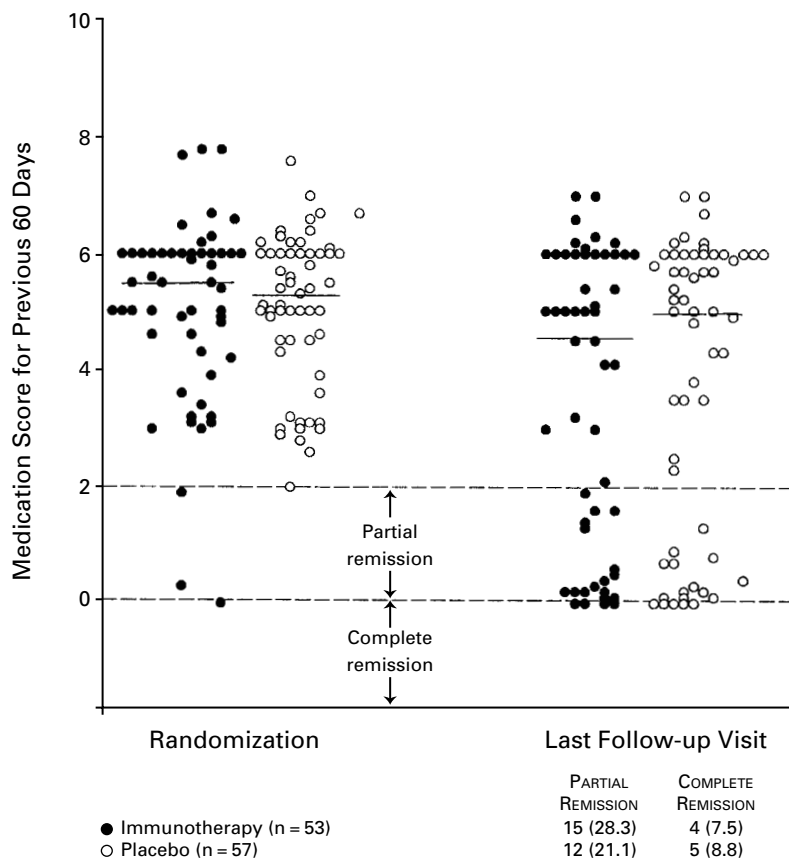


Figure 1. Scores for Daily Medication Use at Randomization and at the Last Follow-up Visit in 110 Allergic Children with Asthma Who Completed at Least 18 Months of Maintenance Treatment after Being Randomly Assigned to Receive Immunotherapy with Broad-Spectrum Allergens or Placebo.

Scores were based on medication use during the 60 days before randomization and before the last follow-up visit. Bars indicate median values for each group. Numbers below the graph are numbers (and percentages) of patients. The rates of partial and complete remission (see the Results section for definitions) did not differ significantly between the two groups.

Other Outcomes

Other clinical outcomes are shown in Table 3. Both groups had significant reductions in symptom scores. The immunotherapy group also had a significant reduction in the use of inhaled corticosteroids, reflecting the same general improvement in asthma indicated by the medication scores. Although the difference in the peak expiratory flow rate between the two groups approached significance, the estimated treatment effect was quite small (a mean difference of 3.8 percentage points in the predicted value in favor of immunotherapy, $P=0.05$). There were no significant differences between the treatment groups in any other outcomes.

In parallel with a decrease in medication requirements, bronchial sensitivity to methacholine decreased (the PC_{20} increased) over time in both treatment groups ($P<0.01$) (Table 3). However, immunotherapy had no specific effect on methacholine sensitivity ($P=0.99$).

Subgroup Analyses

Despite the absence of an effect of immunotherapy on daily medication use, we performed subgroup analyses of medication use to determine tentatively whether certain subgroups of patients benefited from immunotherapy. The study groups were subdivided according to the base-line medication score (as an indication of initial severity of asthma), age, total serum IgE level, and number of treatment allergens received (Table 4). Other variables of interest included the presence or absence of sensitivity to dust mites, the use or nonuse of corticosteroids initially, the quality of immunotherapy (optimal or less than optimal), sex, and race. Of the variables examined, only a younger age (≤ 8.5 years, $P=0.02$; P for interaction = 0.03) and mild asthma (medication score, ≤ 5 ; $P=0.19$) approached statistical significance as factors suggesting a treatment effect in favor of immunotherapy. Neither the duration of the run-in period nor the duration of fol-

TABLE 3. CHANGES IN OUTCOME MEASURES FROM BASE LINE TO THE LAST FOLLOW-UP VISIT.*

MEASURE	PLACEBO (N=60)	IMMUNOTHERAPY (N=61)	MEAN DIFFERENCE (PLACEBO VS. IMMUNOTHERAPY)	95% CI	P VALUE
	mean ±SD				
Medication score					
Base line	5.0±1.3	4.9±1.8	0.11	-0.45 to 0.68	0.99
Change	-1.2±2.0	-1.4±1.9	0.22†	-0.48 to 0.92	0.37
P value	<0.001	<0.001			
Use of corticosteroids (no. of days in previous 60 days)					
Inhaled					
Base line	20.1±24.9	21.4±26.0	1.3	-10.5 to 7.9	0.82
Change	-5.4±27.8	-10.1±24.0	4.7†	-4.7 to 14.0	0.26
P value	0.16	<0.001			
Oral					
Base line	4.4±10.8	5.3±13.3	-0.9	-5.3 to 3.4	0.87
Change	-1.7±12.1	-1.9±12.4	0.1†	-4.2 to 4.5	0.49
P value	0.75	0.19			
PEFR (% of predicted value)					
Base line	84.8±8.6	81.9±10.8	2.9	0.6 to 6.4	0.17
Change	-1.4±11.1	2.5±11.1	-3.8†	-7.8 to 0.1	0.05
P value	0.11	0.24			
Symptom score					
Base line	0.37±0.35	0.34±0.27	0.03	-0.09 to 0.14	0.98
Change	-0.16±0.39	-0.08±0.34	-0.08	-0.21 to 0.05	0.50
P value	0.003	0.02			
Medical contact (no. in previous 60 days)					
Telephone					
Base line	0.37±0.76	0.36±0.61	0.01	-0.24 to 0.25	0.60
Change	-0.22±0.88	-0.05±0.92	-0.17	-0.49 to 0.16	0.60
P value	0.09	0.29			
Office visit					
Base line	0.03±0.18	0.05±0.28	-0.02	-0.08 to 0.04	>0.99
Change	0.00±0.26	-0.03±0.31	0.03†	-0.07 to 0.14	0.71
P value	>0.99	0.75			
Emergency room					
Base line	0.03±0.18	0.08±0.33	-0.05	-0.14 to 0.05	0.41
Change	-0.02±0.37	-0.05±0.38	0.03†	-0.08 to 0.15	0.73
P value	>0.99	>0.53			
Hospitalization					
Base line	0.20±0.90	0.11±0.64	0.09	-0.19 to 0.36	0.63
Change	-0.10±0.77	-0.11±0.64	0.01†	-0.24 to 0.27	0.43
P value	0.63	0.50			
Methacholine sensitivity (mg/ml)‡					
Base line	0.32±0.32	0.23±1.33	0.10	-0.25 to 0.45	0.93
Change	0.39±1.51	0.41±1.87	-0.02†	-0.66 to 0.61	>0.99
P value	0.003	0.008			

*P values for changes within the groups were calculated by applying the Wilcoxon signed-rank test to the ranked changes in each listed variable. P values for the mean differences between the placebo and immunotherapy groups were calculated with the Wilcoxon rank-sum test. CI denotes confidence interval, and PEFR peak expiratory flow rate. Observations were for the 60 days before randomization and before the last follow-up visit.

†The difference is in the direction of a positive effect of immunotherapy.

‡Sensitivity to methacholine was defined as the interpolated concentration of methacholine provoking a 20 percent reduction in the forced expiratory volume in one second.

low-up affected the outcome (P=0.5 and P=0.6, respectively; data not shown).

Immunologic Outcomes

Immunotherapy was associated with a significant increase in the level of allergen-specific IgG antibody. IgG antibody to *Dermatophagoides pteronyssinus* allergens increased from a mean (±SE) of 1.7±0.4 µg per milliliter before immunotherapy to

5.7±1.0 µg per milliliter at the last follow-up visit in the 46 children in the immunotherapy group who received mite allergens. Among the 49 mite-sensitive children in the placebo group, mite-specific IgG levels did not change significantly (2.3±1.8 µg per milliliter at base line and 1.8±0.4 µg per milliliter at the last follow-up visit). The results were similar for short ragweed, grass, oak, and *D. farinae*. On average, the levels of IgG allergen antibodies were 8.8

times higher at the last follow-up visit than at base line in the immunotherapy group and were unchanged in the placebo group. In addition, the mean wheal diameters on skin-prick tests for treatment allergens were reduced substantially (61.3 ± 2.7 percent) in the immunotherapy group but by only 3.8 ± 3.8 percent in the placebo group.

Treatment-Related Adverse Events

Apparent systemic reactions to injections occurred in 21 of the 61 children in the immunotherapy group (34 percent) and in 4 of the 60 in the placebo group (7 percent) ($P < 0.001$). There were 114 systemic reactions in all, 52 of which were treated with adrenergic drugs; all 52 responded to treatment, without clinical sequelae. The rate of systemic reactions in the immunotherapy group was 2.6 per 100 injections.

DISCUSSION

In this study, allergic children with asthma were treated according to a protocol designed to approximate current U.S. standards for immunotherapy, but we were unable to demonstrate any effect of allergen injections on the course of the asthma over a period of 30 months. The principal end point was daily medication use, and all but one of the secondary disease indicators (symptom scores, use of corticosteroids, medical contacts, and remission rates) were similar in the two treatment groups. The peak flow increased slightly in the immunotherapy group and decreased slightly in the placebo group (difference, 3.8 percentage points; $P = 0.05$).

Because our negative findings are contrary to widely held clinical opinion and the results of some studies of asthma and single allergens,¹⁴⁻²¹ we must consider possible explanations for our failure to demonstrate the efficacy of immunotherapy. One possible reason is the selection of patients with disease that is not sufficiently severe to allow the detection of treatment effects. However, two thirds of our patients continued to require daily medication for asthma at the end of the study, and 73 percent of them had severe bronchial hyperresponsiveness according to the criteria established by an international workshop.²²

Another possibility is that overmedication masked an effect of immunotherapy. The study design incorporated an algorithm that forced the physicians, who were unaware of the treatment assignments, to consider a reduction in medication whenever the symptom scores and peak-flow values were in an acceptable range. In both groups, the physicians frequently used clinical judgment and refrained from reducing medications when prompted by the algorithm to do so (53 percent of the time in the immunotherapy group and 45 percent of the time in the placebo group). Nevertheless, over time, medica-

TABLE 4. CHANGES IN MEDICATION SCORES WITHIN SUBGROUPS OF PATIENTS.

SUBGROUP (% OF PATIENTS)	MEAN DIFFERENCE IN MEDICATION SCORE (PLACEBO VS. IMMUNOTHERAPY)*	P VALUE†	P VALUE FOR INTERACTION‡
Base-line medication score			0.19
≤5 (48)	0.69§	0.19	
>5 (52)	-0.25	0.94	
Sex			0.46
Male (68)	0.36§	0.25	
Female (32)	-0.11	0.92	
Race			0.13
White (54)	-0.32	0.72	
Nonwhite (46)	0.85§	0.10	
Age at entry			0.03
≤8.5 yr (40)	1.21§	0.02	
>8.5 yr (60)	-0.42	0.52	
No. of treatment allergens			0.61
≤5 (56)	0.31§	0.35	
>5 (44)	-0.05	0.94	
Base-line serum total IgE level			0.33
≤858 ng/ml¶ (50)	-0.13	0.92	
>858 ng/ml (50)	0.60§	0.17	
Sensitivity to dust mites			0.90
No (77)	-0.11	0.79	
Yes (23)	0.24§	0.47	
Base-line use of inhaled or oral corticosteroids			0.56
No (64)	0.41§	0.31	
Yes (36)	-0.07	0.78	
Quality of immunotherapy			0.47
Optimal (79)	-0.21	0.43	
Less than optimal (21)	1.01§	0.17	

*Mean differences were calculated as the differences in the mean changes from base line to the last follow-up visit in the medication scores between the placebo group and the immunotherapy group.

†P values were determined by applying the Wilcoxon rank-sum test to the ranked changes from the base-line medication scores for each subgroup.

‡P values for interactions were calculated with a rank transformation and two-way analysis of variance; significantly small P values indicate nonequivalent effects of immunotherapy between subgroups. Also analyzed but not shown were the effects of mold immunotherapy ($P = 0.89$), duration of follow-up ($P = 0.47$), and duration of the run-in phase ($P = 0.21$).

§The difference is in the direction of a positive effect of immunotherapy.

¶The median value was 858 ng per milliliter.

||Immunotherapy of optimal quality was defined as the administration of a full maintenance dose for more than 18 months.

tions were withdrawn and the children in both groups did well, as evidenced by the significant declines in medication scores. In addition, 34 children were taking no medications at the end of the study, indicating that the effort to reduce medications during the study was successful.

A third possibility is that the allergen extracts were of poor quality or given in insufficient doses. We chose an allergen supplier (ALK Laboratories, Copenhagen, Denmark) known for its early advocacy of allergen standardization. Where the allergen content was measurable in the extracts used (Table 2), the maintenance dose achieved in 80 percent of the children in the immunotherapy group ranged from 4.3

to 26 μg per injection. Such doses have marked clinical and biologic effects in the treatment of both rhinoconjunctivitis and asthma.^{23,24} Finally, in the immunotherapy group we observed two of the immunologic correlates of high-dose immunotherapy: a mean 8.8-fold increase in the level of IgG allergen antibodies and a 61 percent mean reduction in wheal diameters on skin-prick testing. It therefore seems unlikely that the study failed because of substandard treatment. Another factor pointing to the biologic potency of the allergen regimen was the 2.6 percent rate of systemic reactions, which is similar to that in other studies of high-dose immunotherapy with positive outcomes.^{3,25}

The participants in our study were not typical of allergic children treated for asthma in routine clinical practice. Our patients were selected for compliance during a long run-in period of observation and stabilization. The children and their parents were instructed in the management of asthma and environmental control, and the children were seen every two to three weeks for medication adjustments. We noted substantial improvement in the control of asthma in many children even before randomization. These measures, coupled with the benefit of standard pharmacotherapy, including inhaled corticosteroids in sufficient quantities to control symptoms and maintain peak flows within normal limits, may have controlled the disease process to such an extent that it would have been difficult to show the clinical benefit of any of a number of relatively weak but nevertheless effective therapies, such as inhaled cromolyn or bronchodilators. The results might be different in a pharmacologically undermedicated population with a lower level of compliance and less intensive management. Indeed, there is ample evidence from well-conducted clinical trials of single allergens that immunotherapy provides protection against an allergen challenge and can reduce symptoms or medication requirements, or both.^{5,6} We believe that the results of our study should not be interpreted as indicating that allergen immunotherapy is ineffective in the sense that it cannot reduce sensitivity to treatment allergens. Furthermore, our results are not necessarily inconsistent with prior studies showing the clinical efficacy of single-allergen immunotherapy in some patients with allergic asthma.

What, then, are the implications of our study for the use of immunotherapy in patients with asthma? Allergen immunotherapy is probably not a useful adjunct in the management of moderate-to-severe, perennial allergic asthma, even though it provides protection against specific allergic challenges. It is possible that immunotherapy adds little to modern pharmacotherapy or that allergic triggers for asthma are not as etiologically important as other factors (e.g., viral infections) in asthmatic children who receive instruction in the environmental control of

asthma and intensive pharmacologic therapy, with frequent follow-up visits.

Immunotherapy may still be useful in populations that have lower levels of compliance with pharmacotherapy and self-management procedures than the one we studied or as an alternative to inhaled corticosteroids, which were recently reported to suppress linear growth in children.²⁶ It is also possible that the prophylactic use of immunotherapy early after the onset of asthma alters the natural history of the disease by suppressing airway inflammation at a time when a child is only intermittently symptomatic. It is noteworthy that in our study, the only subgroups in which there was a trend toward a benefit of immunotherapy were the children with milder disease (medication score, ≤ 5 ; and no use of inhaled corticosteroids), and the younger children (age, ≤ 8.5 years), which could reflect a shorter duration of disease. Future investigations should focus on the potential prophylactic use of immunotherapy in children with allergic rhinitis, who are at high risk for asthma, or in highly allergic children with the recent onset of mild asthma.

Supported by a grant from the National Institute of Allergy and Infectious Diseases (AI 21073).

We are indebted to the following drug companies for their contributions: ALK (diagnostic and treatment extracts), Clement-Clarke (peak-flow meters), Schering/Key Pharmaceuticals (albuterol, beclomethasone, and theophylline), Fisons Pharmaceuticals (cromolyn sodium), Upjohn Pharmaceuticals (methylprednisolone), and Boehringer Ingelheim (metaproterenol); to Baruch Friedman, M.D., Jyothi Gadde, M.B., B.S., Kim-Lien Nguyen, M.D., George Philip, M.D., Jacqueline A. Pongracic, M.D., Yong-Hsiung Tsai, M.D., and Robert Wood, M.D., for assistance with the care of the patients in this study; to the numerous referring physicians; to Karen Huss, D.N.Sc., for assistance with environmental assessments; to Kathy Pessaro for clerical support; to James Hull for data management; and to the eight clinical coordinators who managed the protocol during its 10-year life.

REFERENCES

- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-3.
- Cooke RA. Hay fever and asthma: the uses and limitation of desensitization. *N Y Med J* 1918;107:577-83.
- Coleman JW, Davies RJ, Durham SR. Allergen immunotherapy for seasonal and perennial allergic rhinitis. In: BSACI position paper on allergen immunotherapy. *Clin Exp Allergy* 1993;23:Suppl 3:3-6.
- Malling H-J, Weeke B, eds. Position paper: immunotherapy. *Allergy* 1993;48(14):Suppl:9-35.
- Bousquet J, Michel F-B. Specific immunotherapy in asthma: is it effective? *J Allergy Clin Immunol* 1994;94:1-11.
- Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-74.
- Gern JE, Eggleston PA, Schuberth KC, et al. Peak flow variation in childhood asthma: a three-year analysis. *J Allergy Clin Immunol* 1994;93:706-16.
- Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children — a 14-year study. *Pediatrics* 1968;42:793-802.
- Chai H, Farr RS, Froehlich LA, et al. Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975;56:323-7.
- Weiss ME, Wheeler B, Eggleston P, Adkinson NF Jr. A protocol for performing reproducible methacholine inhalation tests in children with moderate to severe asthma. *Am Rev Respir Dis* 1989;139:67-72.

11. Altman DG. Practical statistics for medical research. New York: Chapman & Hall, 1991.
12. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and non-parametric statistics. *Am Stat* 1981;35:124-9.
13. SAS/STAT user's guide, version 6. 4th ed. Cary, N.C.: SAS Institute, 1989.
14. Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. *Lancet* 1954;1:1055-7.
15. Warner JO, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitisation to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* 1978;2:912-5.
16. Smith AP. Hyposensitisation with *Dermatophagoides pteronyssinus* antigen: trial in asthma induced by house dust. *BMJ* 1971;4:204-6.
17. D'Souza ME, Pepys J, Wells ID, et al. Hyposensitization with *Dermatophagoides pteronyssinus* in house dust allergy: a controlled study of clinical and immunological effects. *Clin Allergy* 1973;3:177-93.
18. Ohman JL Jr, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma: double-blind trial with evaluation of in vivo and in vitro responses. *J Allergy Clin Immunol* 1984;74:230-9.
19. Sundin B, Lilja G, Graff-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. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Immunotherapy for cat asthma. *J Allergy Clin Immunol* 1988;82:1055-68.
21. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501-6.
22. Hargreave FE, Woolcock AJ. Airway responsiveness: measurement and interpretation. Mississauga, Ont.: Astra Pharmaceuticals Canada, 1985:84.
23. Lockey RF, Bukantz SC, eds. Allergen immunotherapy. New York: Marcel Dekker, 1991:195-6.
24. Norman PS. Immunotherapy. In: Melillo G, Norman PS, Marone G, eds. Respiratory allergy. Vol. 2 of Clinical immunology. Toronto: B.C. Decker, 1990:3-15.
25. Norman PS, Van Metre TE Jr. The safety of allergenic immunotherapy. *J Allergy Clin Immunol* 1990;85:522-5.
26. Doull IJ, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.