

RAGWEED IMMUNOTHERAPY IN ADULT ASTHMA

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Abstract Background. Although allergen immunotherapy is effective for allergic rhinitis, its role in treating asthma is unclear.

Methods. We examined the efficacy of immunotherapy for asthma exacerbated by seasonal ragweed exposure. During an observation phase, adults with asthma who were sensitive to ragweed kept daily diaries and recorded peak expiratory flow rates between July and October. Those who reported seasonal asthma symptoms and medication use as well as decreased peak expiratory flow were randomly assigned to receive placebo or ragweed-extract immunotherapy in doses that increased weekly for an additional two years.

Results. During the observation phase, the mean (\pm SE) peak expiratory flow rate measured in the morning during the three weeks representing the height of the pollination season was 454 ± 20 liters per minute in the immunotherapy group and 444 ± 16 liters per minute in the placebo group. Of the 77 patients who began the treatment phase, 64 completed one year of the study treatment and 53 completed two years. During the two treatment years, the mean peak expiratory flow rate was higher in the immunotherapy group (489 ± 16 liters per minute, vs. 453 ± 17

in the placebo group [$P=0.06$] during the first year, and 480 ± 12 liters per minute, vs. 461 ± 13 in the placebo group [$P=0.03$] during the second). Medication use was higher in the immunotherapy group than in the placebo group during observation and lower during the first treatment year ($P=0.01$) but did not differ in the two groups during the second year ($P=0.7$). Asthma-symptom scores were similar in the two groups ($P=0.08$ in year 1 and $P=0.3$ in year 2). The immunotherapy group had reduced hay-fever symptoms, skin-test sensitivity to ragweed, and sensitivity to bronchial challenges and increased IgG antibodies to ragweed as compared with the placebo group; there was no longer a seasonal increase in IgE antibodies to ragweed allergen in the immunotherapy group after two years of treatment. Reduced medication costs were counterbalanced by the costs of immunotherapy.

Conclusions. Although immunotherapy for adults with asthma exacerbated by seasonal ragweed exposure had positive effects on objective measures of asthma and allergy, the clinical effects were limited and many were not sustained for two years. (N Engl J Med 1996;334:501-6.)

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THE efficacy of allergen immunotherapy in allergic rhinitis has been repeatedly demonstrated, and the technique is widely used.^{1,2} Immunotherapy in allergic asthma continues to be controversial, however; despite studies of immunotherapy with grass pollen, ragweed pollen, cat dander, and dust mites that have consistently shown objective reductions in the sensitivity of people with allergic asthma, as measured by skin tests and bronchial challenges with allergen extracts.^{1,2} Immunotherapy induces IgG protective antibodies, down-regulates T-cell responses, and inhibits inflammatory responses to challenges with allergens.^{3,4} In people who are allergic to cats, it also reduces responses to cat allergen or to live cats.^{5,6} Nevertheless, such objective measures are not always accompanied by significant improvement in scores based on symptom diaries, perhaps because symptom diaries

are both subjective and imprecise. Furthermore, bronchodilators and inhaled steroids provide reasonable control of symptoms for many people with asthma.

In this article we report a study of immunotherapy with a common seasonal allergen, ragweed pollen, in patients with asthma. In a double-blind, randomized, placebo-controlled study in adults, the key measures were objective (peak expiratory flow rates measured twice daily) and clinical (scores based on symptom diaries and medication use). Secondary measures were skin tests, assessments of allergen-specific antibodies, and allergen and methacholine challenges.

METHODS

Patients

Three health and research centers near the Johns Hopkins University School of Medicine in Baltimore and four centers near the Mayo Clinic in Rochester, Minnesota, recruited patients. Subjects volunteered and gave informed consent before participating. The protocol and consent forms were approved by appropriate review boards at each institution.

Screening

Screening included a medical history and physical examination, prick tests of reactions to aeroallergens (pollen from ragweed, grasses [timothy, June], and trees [oak, maple, elm]); molds [alternaria, cladosporium]; dust mites [*Dermatophagoides farinae*, *D. pteronyssinus*]; cats; dogs; and cockroaches), pulmonary-function tests, and bronchial challenges with ragweed extract and methacholine.

To enter the study, subjects had to be 16 to 70 years old and had to

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have had asthma for at least one year, with exacerbations during the fall season requiring medication, a positive skin-test reaction to ragweed with less reactivity to concomitant and possibly confounding allergens, and a drop of 20 percent in forced expiratory volume in one second after inhaling methacholine at a volume of less than 25 mg per milliliter.

The criteria for exclusion were as follows: asthma requiring two or more hospitalizations in the previous year, inability to be weaned from long-term oral steroids or cromolyn, sensitivity to animals on regular exposure, current smoking, immunotherapy in the past three years or previous ragweed immunotherapy, systemic illness, pregnancy, and inability to undergo diagnostic tests.

Observation Phase

Patients maintained diaries in which they recorded symptoms of asthma and rhinitis (twice a day), medications, and peak expiratory flow rates from July 1 through October 31. Medications were adjusted every three weeks. Daily aeroallergens were sampled in Rochester, Minnesota, and Baltimore with the use of an Ogden rotoslide sampler (Sampling Technologies, Minnetonka, Minn.), which measures daily pollen counts.

Criteria for Entering the Treatment Phase

To enter the treatment phase, patients had to have the following during the ragweed season: worsening asthma-symptom scores, worsening peak expiratory flow rates, and worsening medication scores. They also had to return 80 percent or more of their diary cards.

Ragweed Extract

Lyophilized extract of short-ragweed pollen (Greer Laboratories, Lenoir, N.C.) contained 2170 μg of the principal allergenic protein of ragweed, Amb a 1 (antigen E), or 1 million allergy units per 10 milliliters after reconstitution. Dilutions in phosphate-buffered saline with 0.5 percent human serum albumin and 0.4 percent phenol were prepared by the Mayo Clinic Laboratory.

Treatment Phase

In the double-blind treatment phase, patients received ragweed immunotherapy or placebo injections. Seasonal diaries and clinic visits were continued. Blood to be screened for IgG and IgE antibodies to ragweed was drawn before and after each ragweed season.

The patients in the immunotherapy group received an initial dose of 0.05 ml of a 1:10,000 dilution of ragweed extract (0.001 mg of Amb a 1), which was doubled every week until the maximally tolerated dose or 0.5 ml of the 1:10 dilution (10 μg of Amb a 1) was reached. The patients in the placebo group received injections of placebo that were similarly increased from 0.05 ml to 0.5 ml. Maintenance doses were then administered to each group every two weeks for three months and thereafter every four weeks. After two years of immunotherapy or placebo injections, patients underwent skin-prick testing,⁷ pulmonary-function testing, and bronchial challenges with ragweed and methacholine.

The protocol called for a maintenance dose equivalent to 10 μg of Amb a 1 per injection to be achieved over a period of 19 weeks. Since injections in year 1 did not begin until May 15, patients received only 16 or 17 injections during the 3.5 months before the ragweed season began (mean dose, approximately 4 μg of Amb a 1). In year 2, the mean dose was increased to approximately 10 μg of Amb a 1.

Statistical Analysis

The scoring system is explained in the legend to Figure 1. Statistical analyses included repeated-measures analysis of variance to evaluate changes over time between groups; an analysis of covariance to evaluate post-treatment differences, with adjustment for pretreatment values; repeated-measures analysis of variance with time-dependent covariance to look at differences between the groups over a period of a year, with adjustment for the base-line year; a chi-square test, a Fisher's exact test, and McNemar's test for categorical comparisons and proportions; and for a global evaluation of "asthma," a chi-square test with a Bonferroni adjustment applied to the P values for the three key

tests of clinical asthma.⁸ Data from the diaries were analyzed with the use of a square-root transformation. Data on IgG and IgE antibodies, challenge tests, and skin-test sensitivity were analyzed with the use of a logarithmic transformation.

RESULTS

Demographic Characteristics

Approximately 1000 patients were screened. Ninety of the 127 patients who entered the observation phase met the criteria for entering the treatment phase. They were assigned to receive ragweed immunotherapy or placebo according to computer-generated random numbers at the central statistical office in Cincinnati. Before treatment was initiated in May, 13 people dropped out. Of the 77 patients who began the treatment phase, 64 completed one full year of treatment and 53 completed two full years.

Table 1 shows the demographic characteristics of the patients, which were similar in the two groups. Of the patients who entered the treatment phase, eight in the immunotherapy group dropped out: four moved, three withdrew, and one became pregnant. Sixteen patients in the placebo group dropped out: 3 moved, 11 withdrew, 1 discontinued the study treatment because of worsening asthma, and 1 because of a possible adverse reaction. Patients in the two groups who remained after two years were still demographically similar (data not shown).

Pollen Count

Ragweed counts in Rochester and Baltimore were similar during the observation phase (peak range, 300 to 600 pollen grains per cubic meter) and during the two treatment years (peak range, 600 to 1500 pollen grains per cubic meter). Ragweed pollination occurred approximately one week earlier in Rochester than in Baltimore. Pollen counts from Rochester were representative of the north-central health centers and those from Baltimore were representative of the centers in Baltimore, Washington, D.C., and northern Virginia.

Peak Expiratory Flow Rates

During the observation phase, the peak expiratory flow rate of each group fell during the ragweed season (Fig. 1A). During the treatment phase, peak flows measured in the morning stayed the same or increased in the immunotherapy group during the peak weeks of the pollen season, whereas these rates fell in the placebo group. During the three weeks of peak pollination during the observation phase, the mean (\pm SE) daily peak flow was 454 ± 20 liters per minute for patients in the immunotherapy group and 444 ± 16 liters per minute for those in the placebo group. During the two treatment years, these values were 489 ± 16 and 453 ± 17 liters per minute during the first year ($P=0.06$) and 480 ± 12 and 461 ± 13 liters per minute during the second ($P=0.03$). Evening peak flows were consistently higher than morning measurements, but the findings were similar ($P=0.06$ and $P=0.01$, respectively). Seventeen patients were followed for a third treatment year.

In this subgroup, the peak expiratory flow rate was 495 ± 22 liters per minute for nine patients in the immunotherapy group and 455 ± 20 liters per minute for eight patients in the placebo group ($P = 0.05$).

Medication Use

The mean daily score for asthma medication in both groups before ragweed pollination started (Fig. 1B) indicated moderate to severe asthma, according to published guidelines.¹¹ Both groups showed a continuing reduction in medication use over the three seasons of the study. Medications were adjusted by a physician every three weeks during the period in which diaries were kept. The medication score was higher (indicating a greater use of medication) for the immunotherapy group than for the placebo group during the observation phase (33 ± 7 vs. 28 ± 4). This was reversed during the first treatment year (19 ± 8 vs. 43 ± 8 , $P = 0.01$). The immunotherapy group had a reduction in the use of both inhaled steroids and inhaled bronchodilators (data not shown). There was no significant difference between the groups in medication use during the second treatment year (29 ± 8 vs. 33 ± 8 , $P = 0.7$), which is the principal distinction between the results for the first and second years.

Symptoms of Asthma

During the observation phase, both groups reported increases in symptom scores from 3 (annoying) to 4 (moderately severe) or 5 (severe) (Fig. 1C). Seasonal symptom scores for the immunotherapy group improved throughout the two seasons of treatment, whereas those for the placebo group showed less improvement. When the two groups were compared, the difference in symptoms was not significant ($P = 0.08$ in year 1 and $P = 0.3$ in year 2).

Overall Evaluation

With the use of the P values shown in Figure 1, a combined chi-square test of peak flow measurements, medication use, and asthma symptoms was significant in the first year ($P = 0.003$; with a Bonferroni correction for multiple evaluations, $P = 0.009$), indicating a significant difference between the two study groups; results for the second year were not significant ($P = 0.1$).

Symptoms of Rhinitis

Patients had symptoms of rhinitis, although they were less severe than in most studies of patients with hay fever who do not have asthma. Rhinitis-symptom scores (measured on the same 6-point scale as the asthma-symptom scores) were 4.5 ± 0.3 for the placebo group and 4.1 ± 0.3 for the immunotherapy group during the observation phase. Scores were 4.3 ± 0.5 and 3.5 ± 0.5 ($P = 0.1$), respectively, in the first treatment year and 3.8 ± 0.5 and 3.1 ± 0.4 ($P = 0.04$) in the second.

Bronchial Provocation by Allergens

During screening, results of both the antigen challenge in 53 patients ($r = 0.92$) and the methacholine

Table 1. Base-Line Characteristics of the 77 Patients Who Began the Treatment Phase.*

CHARACTERISTIC	IMMUNOTHERAPY GROUP	PLACEBO GROUP
No.	37	40
Age — yr	36.0 ± 10.3	35.1 ± 10.9
Male sex — no. (%)	19 (51)	20 (50)
No. of years of asthma	19.2 ± 12.8	16.1 ± 14.7
Peak expiratory flow rate — liters/min	472 ± 123	450 ± 91
Ragweed IgE — ng/ml	56 ± 10	121 ± 31
Skin-test sensitivity — log dilution	-1.2 ± 1.5	-1.6 ± 1.4
Ragweed-challenge result†	-1.4 ± 1.1	-1.5 ± 1.3
Methacholine-challenge result†	-0.9 ± 0.7	-1.1 ± 0.7

*Plus-minus values are means \pm SD.

†Values are the logarithms of the doses that result in a drop of 20 percent in forced expiratory volume in one second. The standardized method described by a committee of the American Academy of Allergy and Immunology was used.^{9,10}

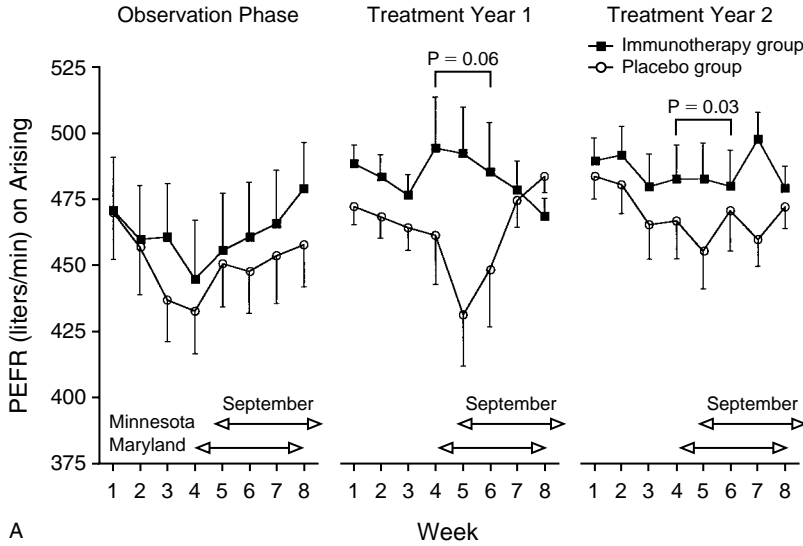
challenge in 56 patients ($r = 0.75$) were reproducible. After treatment, the immunotherapy group had a lower sensitivity to ragweed than the placebo group — that is, the immunotherapy group required significantly more antigen (log micrograms of Amb a 1) to induce a 20 percent drop in forced expiratory volume in one second (-0.273 ± 0.045 , vs. -0.662 ± 0.135 in the placebo group; $P = 0.03$). Eighteen of 26 patients in the immunotherapy group and 11 of 24 in the placebo group had an improvement in antigen sensitivity of at least 0.5 log (a decrease in sensitivity by a factor of 3 or more). There was no difference in pretreatment ragweed sensitivity between the 53 subjects who completed the study and the 37 who dropped out. Preseason sensitivity to methacholine did not decrease (data not shown).

Antibody Responses

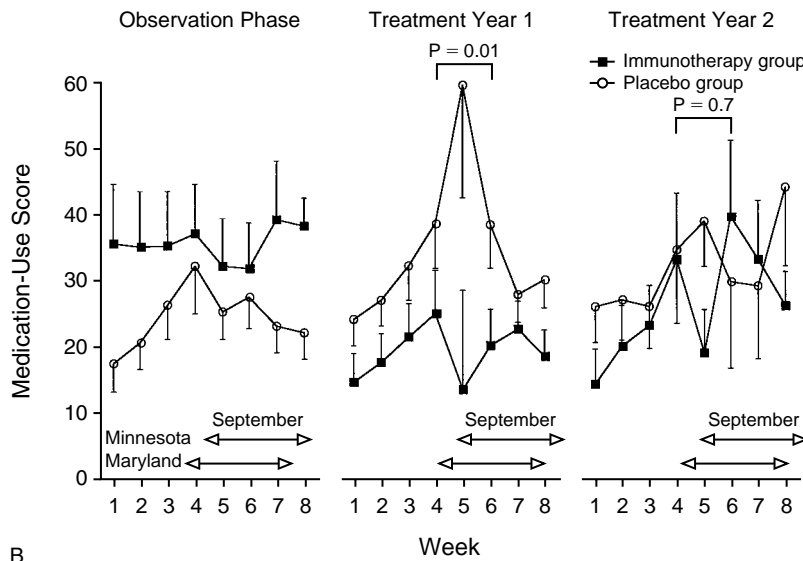
The placebo group had an increase in the levels of IgE antibody to ragweed after each season. The immunotherapy group had lost the seasonal rise in IgE ($P = 0.02$) by the second year of treatment (Table 2). The level of IgG antibody to ragweed was unchanged in the placebo group but increased in the immunotherapy group to a mean of $2700 \mu\text{g}$ per milliliter, indicating that an immunologically adequate dose was administered ($P < 0.001$ by a between-groups repeated-measures analysis of variance).

Skin-Test Sensitivity

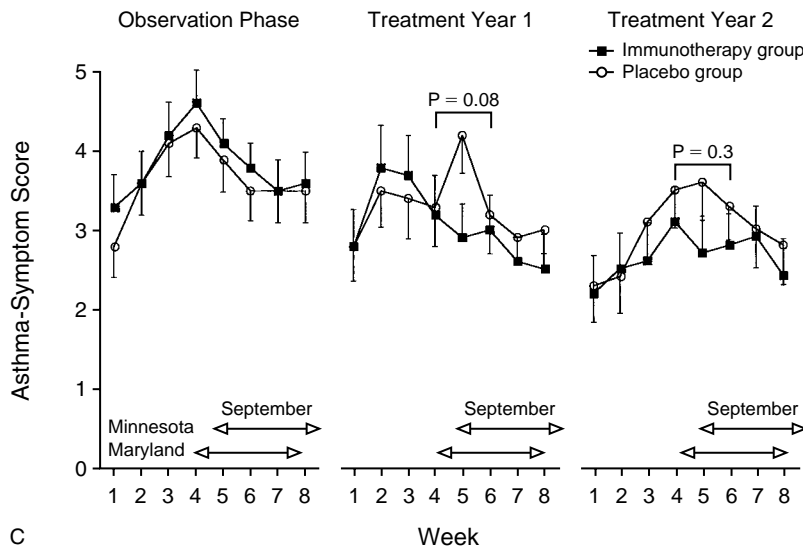
After treatment, the patients in the immunotherapy group had reduced skin-test sensitivity — that is, they required more antigen to elicit a positive skin-test response. In the placebo group, the mean concentration of ragweed extract (log micrograms of Amb a 1 per milliliter) required to elicit an area of erythema 20 to 30 mm in diameter was 0.03 (95 percent confidence interval, 0.0002 to 8.51) before treatment and 0.09 (0.0002 to 42.78) after two years. The corresponding values were



A



B



C

Figure 1. Evaluations of Asthma.

Data from Baltimore have been shifted by one week to make the times of ragweed exposure coincide for the Baltimore and Rochester, Minnesota, areas. The brackets show the significance of the difference between the placebo and the immunotherapy groups in daily measurements or scores for the three weeks of greatest pollen exposure, with the use of an analysis of variance to correct for differences during the observation phase.

Panel A shows the weekly mean (\pm SE) peak expiratory flow rate (PEFR) measured in the morning before, during, and after the ragweed-pollination season. Measurements of peak expiratory flow were recorded (with a mini-Wright peak-flow meter) as the highest of three successive readings of peak flow when patients arose.

Panel B shows the daily mean (\pm SE) medication scores for each week before, during, and after the ragweed-pollination season. Each of the following was scored as 1 unit: 200 mg of short-acting xanthine, 100 mg of long-acting xanthine, 1 puff from a sympathomimetic inhaler, a 2-mg albuterol tablet, a 2.5-mg terbutaline tablet, a 10-mg metaproterenol tablet, 1 puff of ipratropium, a half-puff of inhaled corticosteroid, a half-puff of a nasal corticosteroid, a half-puff of cromolyn, 0.5 mg of prednisone, and 0.4 mg of methylprednisolone. An injection of a bronchodilator was scored as 4 units, and respiratory therapy with a bronchodilator was scored as 4 units plus 1 unit for each 0.25 ml of medication. Antihistamines were not scored.

Panel C shows daily mean (\pm SE) asthma-symptom scores. Symptoms were scored on a 6-point scale (0, none; 1, trivial or doubtful; 2, mild and causing little or no discomfort; 3, annoying but causing no marked discomfort; 4, moderately severe and causing marked discomfort; 5, severe and interfering with sleep or activities but not incapacitating; and 6, incapacitating).

0.06 (0.0001 to 39.3) and 0.7 (0.004 to 123.3) for the immunotherapy group ($P < 0.001$).

Costs of Medication

The costs of medication (retail cost in 1987) were \$597 per season for the placebo group and \$420 for the immunotherapy group. The charges for immunotherapy were \$314 the first year (materials, \$160; injection charges, \$154). The second-year costs for booster injections were \$213 (materials, \$130; injection charges, \$83). We assumed that the cost of medical supervision of medication use alone was the same as that of medication use plus allergy injections. By 1995, dollar costs had increased 43 percent for medications and 54 percent for allergy injections (data not shown).

Untoward Reactions

During treatment year 1, seven patients receiving ragweed extract reported systemic allergic symptoms after injections (on 14 occasions). Five of these reactions were mild and resolved spontaneously; nine consisted of rhinitis, generalized urticaria, angioedema, or some combination of these symptoms and were treated with antihistamines or epinephrine. Two patients receiving ragweed extract dropped out after having several systemic reactions. One patient assigned to the placebo group received an injection of active extract by mistake and had a severe systemic reaction characterized by bronchospasm and hypotension. Recovery with treatment was rapid. Four other patients receiving placebo reported moderate reactions and received treatment. No evidence of treatment error was found in these cases.

DISCUSSION

The fact that the major allergens of ragweed pollen have been characterized in order to standardize extracts¹⁴ and the repeatedly demonstrated efficacy of ragweed immunotherapy in seasonal rhinitis¹⁵ made ragweed a logical choice for a seasonal study. Yet, only 127 of 1000 patients screened met the entry criteria.

Improvement in allergic manifestations after immunotherapy depends on the dose of the allergen. A maintenance dose of 3 to 12 μg of Amb a 1 (1000 to 4000 allergen units per injection) consistently results in a significant improvement in rhinitis caused by allergy to ragweed.¹⁶ Our patients received doses of 4 μg per injection the first year and 10 μg per injection the second year.

The four objective measurements of laboratory, skin, and pulmonary responses to ragweed allergens were significantly different in the immunotherapy and placebo groups. However, differences in the severity of the clinical disease "asthma" were less clear. Of the three clinical indicators, we emphasize measurements of peak expiratory flow because they provide objective day-to-day assessments of the seriousness of asthma. During treatment, the immunotherapy group no longer had a seasonal decline in peak expiratory flow rates, whereas the placebo group continued to have a worsening in these rates. The mean peak expiratory flow rate was 10 liters

Table 2. Seasonal Changes in Ragweed-Specific IgE Antibody.*

STUDY PHASE	PLACEBO GROUP		IMMUNOTHERAPY GROUP	
	PRESEASON	POSTSEASON	PRESEASON	POSTSEASON
Observation phase	121 \pm 31	256 \pm 65	56 \pm 10	93 \pm 16
Treatment year 1	106 \pm 31	211 \pm 69	94 \pm 32	115 \pm 30
Treatment year 2	118 \pm 44	180 \pm 63	71 \pm 18	64 \pm 16†

*Plus-minus values are mean (\pm SE) levels of serum IgE antibodies against ragweed allergens, measured in nanograms per milliliter. The antibodies were measured according to the methods of Hamilton and Adkinson.^{12,13}

†Despite the apparent difference between preseason and postseason values during the observation phase, the increases that occurred initially in both groups disappeared in the immunotherapy group by the second year of treatment ($P = 0.02$ by a between-groups repeated-measures analysis of variance for the changes between preseason and postseason values). Data were log-transformed for analysis because of the non-normality of distribution.

per minute higher in the immunotherapy group than in the placebo group during the observation phase, but 44 liters per minute higher the first year and 17 liters per minute higher the second year. This change in peak flow is similar to the changes observed in the treatment of asthma with various drugs. A study of fluticasone given in moderate doses (100 mg per day) showed a difference of 35 liters per minute¹⁷; a study of nedocromil, a difference of 16.5 liters per minute¹⁸; a study of salmeterol, a difference of 26 liters per minute¹⁹; and a study of zileuton, a 5-lipoxygenase inhibitor, a difference of 24 liters per minute (Liu MC, et al.: personal communication).

In contrast, both groups had some improvement in asthma symptoms during treatment, not only during the ragweed season but in their preseasonal base-line assessments. This suggests the benefit of regular visits with a physician, with careful adjustments of medication doses to alleviate symptoms. The improvement was slightly but not significantly greater in the group receiving immunotherapy. Any reduced medication costs were counterbalanced by the costs of immunotherapy.

The improvement in pulmonary function was not reflected in medication use during the second year. In the placebo group, seasonal medication scores increased progressively over the three years. In the immunotherapy group, they declined in the first treatment year but rose again in the second. As assessed globally according to the three primary criteria, immunotherapy appeared not to be effective the second year. These results are unlike those with immunotherapy for hay-fever allergies, in which progressive improvement over several years is the rule.

The rate of allergic reactions to the injections of ragweed extract in these patients with asthma was similar to that in patients with rhinitis. Patients with asthma appeared to have no greater risk of adverse reactions than those with rhinitis. Severe reactions may nevertheless lead to worse respiratory distress in patients with asthma.

No single study can answer all questions about the place of immunotherapy in the treatment of allergic asthma. Immunotherapy can potentially improve pulmonary responses to an allergen. With effective medications available, we believe only a small percentage of patients with continuing asthma would want to undertake immunotherapy for a single, seasonal allergen that might con-

for a benefit for a few weeks. In the future, immunization for all the allergens to which a patient is sensitive might be studied. Immunotherapy could be individualized to include the relevant allergens, particularly those to which patients are perennially exposed, such as dust mites.

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