

Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite

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Background: Although several studies support the efficacy of specific immunotherapy in allergic asthma, its benefit compared with that of standardized pharmacologic intervention remains unknown.

Objective: A double-blind, placebo-controlled trial in 72 patients with mild-to-moderate asthma and allergy to house dust mite (HDM; *Dermatophagoides* species) was conducted to assess the effects of specific immunotherapy added to guideline-adjusted pharmacologic treatment and allergen avoidance.

Methods: After 1 observational year of pharmacologic treatment and standard measures of HDM avoidance, 2 groups of asthmatic subjects were randomly assigned to receive specific immunotherapy consisting of subcutaneous injections of either a mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* vaccine (n = 41) or placebo (n = 31) for 3 years. Medications were adjusted every 3 months according to the Global Initiative for Asthma guidelines.

Results: The adjustment of treatment was associated with a reduction in asthma symptom scores in all subjects. The addition of specific immunotherapy was associated with a decrease in the number of subjects requiring rescue bronchodilators, an increase in morning and evening peak expiratory flow, and a reduced skin sensitivity to HDM extracts. The addition of specific immunotherapy had no significant effects on the cumulative dose of inhaled corticosteroids, asthma symptoms, lung volumes, or bronchial responsiveness to methacholine.

Conclusion: These results suggest that specific immunotherapy added to pharmacologic treatment and HDM avoidance provides marginal but statistically significant clinical benefits, possibly by reducing the allergic response of asthmatic patients

sensitized to HDM. (*J Allergy Clin Immunol* 2004;113:643-9.)

Key words: Bronchodilators, corticosteroids, allergens, lung function, prevention

House dust mite (HDM) is the most common indoor allergen and a major cause of perennial asthma worldwide.^{1,2} The Global Initiative for Asthma (GINA) guidelines recommend managing allergic asthma with pharmacologic treatment and allergen avoidance. Specific immunotherapy is recommended in mild-to-moderate cases not controlled by pharmacologic treatment and allergen avoidance.³

In patients with perennial asthma caused by HDM allergy, specific immunotherapy may attenuate airway sensitivity to allergens, improve symptoms, reduce asthma medication scores, and, in some cases, reduce nonspecific bronchial hyperresponsiveness.⁴⁻⁷ Although a meta-analysis of several studies confirms the efficacy of immunotherapy in asthma, its benefit compared with that of standardized pharmacologic intervention remains unknown.⁸ The question of whether specific immunotherapy can reduce drug consumption, improve lung function, or both in the majority of patients with allergic asthma who exhibit a satisfactory response to conventional asthma treatment is relevant because specific immunotherapy is usually added to pharmacologic treatment. In a pioneering study, Adkinson et al⁹ administered multiple-allergen immunotherapy to allergic asthmatic children receiving pharmacotherapy for asthma but detected no significant differences compared with placebo injections. We extended the evaluation to adults and carefully selected the subjects to maximize the efficacy of immunotherapy. Our hypothesis was that immunotherapy might improve asthma control through mechanisms different from those of conventional treatment and thus might provide additional benefit. To test this hypothesis, the additive benefit, if any, of specific immunotherapy was investigated in patients with perennial asthma and HDM allergy who were receiving satisfactory medical care, including standard allergen avoidance measures in bedrooms and drug treatment according to international GINA guidelines.³ The main aim of the study was to investigate whether specific immunotherapy is associated with clinical improvement and a significant reduction in antiasthma medication use.

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Supported by a grant from the Regione Veneto, Giunta Regionale, Ricerca Sanitaria Finalizzata, Venezia, and ALK-Abelló S.p.A., Lainate, Milano, Italy.

Received for publication August 20, 2003; revised December 30, 2003; accepted for publication December 31, 2003.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2003.12.586

Abbreviations used

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|------------------------------------------------------------------------------------------------------------------|
| BU: Biologic unit |
| GINA: Global Initiative for Asthma |
| HDM: House dust mite |
| MDI: Metered-dose inhaler |
| PD ₂₀ FEV ₁ : Cumulative dose of methacholine producing a 20% decrease in FEV ₁ |
| PEF: Peak expiratory flow |

METHODS**Subjects**

Ninety-five asthmatic subjects aged 8 to 43 years (32.6% < 18 years old) were recruited from the outpatient clinics of 11 participating centers. The subjects included in the study had the following characteristics:

- a typical history of bronchial asthma for at least 1 year³;
- reversibility of bronchial obstruction (increase in FEV₁ of $\geq 15\%$ after inhaled salbutamol) or bronchial hyperresponsiveness to methacholine challenge;
- sensitization to HDM confirmed on the basis of a positive skin prick test response to HDM extract (ALK-Abellò, Milano, Italy), the presence of serum-specific IgE (\geq class 3), or both to *Dermatophagoides pteronyssinus* (Phadebas RAST; Pharmacia, Uppsala Sweden);
- absence of concomitant sensitization to perennial allergens other than HDM, such as cat, dog, *Alternaria* species, *Aspergillus* species, and cockroach (approximately 80% of the screened population was excluded to meet this criterion because most of them had multiple sensitization); and
- residence in northeast Italy less than 1000 meters of altitude above sea level.

Subjects presenting with at least one of the following characteristics were excluded: respiratory diseases other than asthma; cardiovascular or immunologic diseases or other severe illnesses; active smoking status; FEV₁ persistently less than 70% of predicted value; previous immunotherapy with HDM within 3 years from the start of the study; recurrent asthma exacerbations or more than 2 emergency hospitalizations for an asthmatic attack in the previous year; and work-related symptoms of asthma or occupational asthma.

Informed consent to participate in the study was given by all subjects. The protocol was approved by the ethical committees of the University Hospital of Padova and of other participating centers.

Design of the study

The study design was randomized, double blind, and placebo controlled. Subjects were recruited over a period of 5 months (November through March) and were studied for 4 years. All subjects underwent an initial period of observation and stabilization for 1 year. They were then randomized to receive subcutaneous immunotherapy or placebo for 3 years by an investigator (LZ) independent from the treatment team.

At entry into the study, each subject's asthma severity was assessed, and drug treatment was assigned according to the recommendations of the GINA guidelines.³ Salbutamol (metered-dose inhaler [MDI], 100 μ g per actuation) was used as a bronchodilator. Beclomethasone dipropionate (MDI, 250 μ g per actuation) was used as a regular anti-inflammatory agent. No other antiasthma drugs were allowed, except oral antihistamine tablets (cetirizine) for treatment of rhinitis. Subjects were instructed how to fill in diary cards for assessment of symptoms and medication use and how to

perform peak expiratory flow (PEF) monitoring. In addition, they were given written recommendations of measures for reducing exposure to HDM and were supplied with allergen-impermeable covers (CFB, Nibionno, Italy) to encase mattresses and pillows in their bedrooms.

Clinical assessment was repeated each year in February or March (visit 1), May (visit 2), September or October (visit 3), and December (visit 4). At each visit, diary cards and PEF records were reviewed, spirometric measurements were performed, and drug treatment was modified, if required, according to the severity and clinical activity of asthma. Indicators for a decrease or increase in medication were frequency of symptoms, FEV₁ values, and PEF variability.³ In addition, bronchial provocation testing with methacholine was performed at visit 3. The levels of HDM allergens in the subjects' bedrooms were evaluated in October or November of the observational year and of the first and last years of immunotherapy.

Symptom scores and drug use

The subjects kept diaries for assessment of asthma symptoms and antiasthma drug use during five 4-week periods each year: March, May, September, October, and November. The following scores were recorded daily: nighttime asthma symptoms on a scale from 0 to 3 and daytime asthma symptoms on a scale from 0 to 3.

Intake of antiasthma drugs was recorded as the number of MDI actuations per day.

Mean symptom scores per month and drug use in the autumn months (September, October, and November) were calculated for each subject, and the values were used for comparison of the 2 groups.

PEF monitoring

Subjects were supplied with peak flowmeters (fdE; Ferraris Medical Ltd, London, United Kingdom) and were instructed to measure morning and evening PEF during five 4-week periods each year: March, May, September, October, and November. Subjects were advised not to record PEF for 6 hours after use of short-acting bronchodilator medication.

Pulmonary function tests

Lung function was measured at each visit with a dry spirometer (PFT 922; Sensor Medics, Anaheim, Calif). Subjects were tested at least 12 hours after the last inhaled short-acting bronchodilator. Values were expressed as a percentage of predicted values.¹⁰

Airway responsiveness to methacholine was assessed in subjects whose FEV₁ was greater than 80% of predicted value, as previously described.¹¹ The cumulative dose of methacholine (in micrograms) that produced a 20% decrease in FEV₁ (PD₂₀FEV₁) was calculated by interpolation of the dose-response curve and was used to measure airway responsiveness.

Allergen extracts

The extracts of *D pteronyssinus* and *Dermatophagoides farinae* were standardized according to allergenic potency, major allergen content, and allergenic activity. The biologic activity of the extract was expressed in biologic units (BUs) by the manufacturer (ALK-Abellò, Madrid, Spain). At a concentration of 100 BU/mL, the extract contained 40 μ g/mL Der p 1, 40 μ g/mL Der f 1, and 20 μ g/mL Der 2 (Der p 2 + Der f 2). A 1:1 mixture of *D pteronyssinus* and *D farinae* extracts adsorbed to aluminum hydroxide in normal saline solution with 0.4% phenol was used for immunotherapy. The same batch of extract in different diluents was used throughout the study for diagnostic tests and treatment.

Skin prick test

Skin prick tests were performed with different concentrations of HDM extract (4, 20, and 100 BU/mL) before treatment and after 1, 2, and 3 years of immunotherapy. Positive and negative controls were

histamine (10 mg/mL) and the diluent, respectively. The response was measured after 15 minutes by copying the wheal reaction with transparent adhesive tape onto a record sheet for later computation of the area of the skin reaction.¹²

Immunotherapy

Three consecutively numbered vials of allergen extract containing increasing concentrations of allergen (0.1, 1.0, and 10 BU/mL) were prepared for each subject. Placebo preparations were identical to active solution, including the color, except that they consisted of aluminum hydroxide solution. Histamine (10 mg/mL) was added to half of the placebo vials used during the first and second years of treatment to prevent unblinding because of a lack of any skin reaction at the injection site. Immunotherapy was administered blindly by a treatment team that was also responsible for the assessment and treatment of any adverse reactions. Treatment was initiated with subcutaneous injection of 0.1 mL of a 0.1 BU/mL concentration. Injections were increased weekly to reach a target maintenance dose of 7 BU in adults and 6 BU in children. Maintenance therapy, given every 3 weeks until the completion of the study, consisted of 6 µg/mL major antigens (Der 1 + Der 2).

Domestic dust sampling and analysis

Bedroom dust was collected by means of standardized vacuum cleaning. Each subject's bedding (pillows and quilt), mattress, and bedroom floor were vacuumed by the same technician with the same vacuum cleaner (Folletto, Vorwerk, Germany). In each bedroom, a sampling time of 1 min/m² was applied to both the floor and the mattress. Each sample was sieved and weighed, and 1 g of dust was extracted with 10 mL (10% weight per volume) of PBS, 0.1 mol/L, at pH 7.4.

Der p 1 and Der f 1 were measured with a solid-phase ELISA according to the method described by Ventas et al¹³ with mAbs (Pt1513 and Fa1511; ALK-Abellø, Madrid). Der 2 (Der p 2 + Der f 2) was determined according to the method described by Heymann et al (ALK-Abellø, Madrid).¹⁴ The results were expressed as micrograms of antigen per gram of dust.

Statistical analysis

The primary outcome measures were lung function parameters. The sample size was estimated a priori on the basis of previous experience with PD₂₀FEV₁.¹⁵ Assuming a minimum significant difference of 2-fold methacholine doses, 28 subjects in each group would be required to reject the null hypothesis at the 5% significance level for 90% power. Quantitative data are presented as means ± SDs. Comparison between means was performed with the Student *t* test for unpaired data. Subjects who did not undergo methacholine challenge because of bronchoconstriction were given a PD₂₀FEV₁ arbitrary value of 0.¹⁶ Logarithmic transformation of PD₂₀FEV₁ was used for the analysis, and PD₂₀FEV₁ data were presented as geometric means. Before log transformation, +1 was added to each original PD₂₀FEV₁ value.¹⁷ The analysis of time trend of FEV₁ and PEF data was done by using a mixed-model ANOVA. Because the data of HDM antigens, skin tests, and asthma symptom scores were significantly non-Gaussian, they were expressed as medians. Comparison between groups was performed by using the 2-sample Wilcoxon rank sum test. Comparison of frequencies was performed with the χ^2 test. *P* values of less than .05 were considered significant. Adjustment for multiple comparison was made by using the Bonferroni correction when nonparametric statistics were used. The statistical analysis focused on data collected in September through November because the autumn months in northern Italy are the most favorable for HDM proliferation¹⁸ and usually are associated with more respiratory symptoms in patients allergic to HDM. In addition, in this period of the year, there is no interference from grass pollen exposure. Finally,

TABLE I. Baseline characteristics of 72 subjects with asthma randomly assigned to receive immunotherapy or placebo

| | Placebo (n = 31) | Immunotherapy (n = 41) |
|---------------------------------------------------------|---------------------|---------------------------|
| Sex (M/F) | 22/9 | 25/16 |
| Age (y) | 23.4 ± 9.8 | 20.2 ± 8.1 |
| < 16 y (no.) | 8 | 15 |
| Severity of asthma (mild/moderate) | 16/15 | 21/20 |
| Medications* | | |
| Inhaled corticosteroids† (µg/d) | 0 (0-500) | 20 (0-517) |
| Taking inhaled steroids (no., %) | 14 (45.2) | 21 (51.2) |
| Bronchodilators† (no. actuations/d) | 0.2 (0-0.9) | 0.1 (0-0.6) |
| Allergy to grass pollen (no., %) | 7 (23) | 12 (29) |
| Bedroom mite allergens | | |
| Der p 1 (µg/g dust)† | 5.0 (0.7-13.8) | 2.1 (0.5-8.6) |
| >2 µg/g dust (no., %) | 20 (64) | 21 (51) |
| Der f 1 (µg/g dust)† | 0.8 (0.3-1.5) | 0.9 (0.3-4.3) |
| >2 µg/g dust (no., %) | 4 (13) | 13 (32) |
| Der 2 (µg/g dust)† | 2.1 (0.8-3.6) | 2.1 (0.9-4.5) |
| Morning PEF (% predicted)‡ | 97.2 ± 12.9 | 99.3 ± 14.7 |
| FEV ₁ (% predicted) | 94.4 ± 15.8 | 97.4 ± 15.7 |
| PD ₂₀ FEV ₁ (µg methacholine)§ | 95 (44-203) | 158 (91-274) |

Quantitative data are expressed as means ± SDs. None of the baseline variables differed significantly between the 2 groups.

*Average use in September through November before randomization.

†Median (interquartile range).

‡Mean value over a 30-day period before randomization.

§Geometric mean (95% CI).

these months correspond to the period when bedroom dust was collected and methacholine challenge was performed.

RESULTS

The baseline characteristics of the 72 subjects who completed the study are reported in Table I. The groups did not differ in any of the variables listed.

Of the 95 subjects randomized, 23 dropped out before the completion of the study (15 in the placebo group and 8 in the active treatment group). Ten subjects dropped out early, between 2 and 8 months after randomization, and the remaining 13 dropped out after more than 1 year of treatment. The reasons for dropping out were pregnancy (n = 4), movement out of the area (n = 3), noncompliance (n = 7 in the placebo group and n = 3 in the active treatment group), family problems (n = 3), and symptoms (n = 3). Treatment injections were not related to the symptoms inducing the dropouts, except for in one subject in the placebo group who had subcutaneous nodules at the site of injections. Thirty-six (88%) of the 41 subjects in the immunotherapy group and 29 (94%) of the 31 subjects in the placebo group received the target maintenance dose. Injections were, in general, well tolerated. No anaphylactic reactions or generalized urticaria were observed.

TABLE II. Levels of HDM antigens in the bedroom dust collected during the study period in subjects' houses

| | Placebo | Immunotherapy |
|---------------------------------|----------------|----------------|
| Der p 1 ($\mu\text{g/g}$ dust) | | |
| Observational year | 5.0 (0.7-13.8) | 2.1 (0.5-8.6) |
| Year 1 | 2.7 (0.7-9.8) | 2.2 (0.4-13.6) |
| Year 3 | 4.3 (1.5-9.0) | 3.8 (0.8-18.7) |
| Der f 1 ($\mu\text{g/g}$ dust) | | |
| Observational year | 0.8 (0.3-1.5) | 0.9 (0.3-4.3) |
| Year 1 | 0.3 (0.1-1.2) | 0.6 (0.2-2.1) |
| Year 3 | 1.0 (0.6-2.9) | 1.6 (0.7-3.3) |

Data are presented as medians (interquartile ranges).

Bronchospasm was reported on only 2 occasions during the induction phase in the immunotherapy group and did not require medical attention; in both cases it was reversed by means of self-administered inhaled salbutamol.

The content of HDM allergens in the bedroom dust of subjects' houses did not change significantly during the study period (Table II). Immunotherapy was associated with a significant decrease in skin sensitivity to HDM extract, whereas there was a trend toward increasing skin reaction to the allergen in the placebo group (Fig 1).

Morning and evening PEF values improved significantly in the immunotherapy group but did not change in the placebo group (Fig 2, evening PEF values not shown). The average increase in the immunotherapy group was between 1.6% and 4.7% in the predicted value of morning PEF and between 2.5% and 5.5% in the predicted value of evening PEF during the autumn months of the last year of the study. Median asthma symptom scores in both the placebo and immunotherapy groups tended to decrease during the study, but the changes were not statistically significant (Fig 3). A difference in asthma symptom scores between the 2 groups in the second year of treatment was not confirmed at the end of the study. The proportion of subjects who did not use bronchodilators during the autumn months increased significantly from the observational year to the third year of treatment in the immunotherapy group but not in the placebo group (Table III). No significant change in the average use of inhaled steroids and bronchodilators was observed in the 2 groups after randomization.

No significant differences in FEV₁ (data not shown) or in degree of bronchial responsiveness (as indexed by the PD₂₀FEV₁; Table IV) were detected between the 2 groups at any visit. Analyses of the 2 subgroups (age [both pediatric and adult] and initial severity of asthma [both mild and moderate]) did not modify the outcome of the study. No significant differences in the outcome variables (PEF, symptoms, and drug records) were observed during March and May compared with during the autumn months (data not shown).

DISCUSSION

In this study the addition of specific immunotherapy to pharmacologic treatment and allergen avoidance was

associated with a reduced use of rescue bronchodilators, a progressive increase in morning and evening PEF values, and a reduced skin reactivity to HDM extracts. These results suggest that specific immunotherapy added to appropriate medical care provides marginal but statistically significant additional clinical benefits, possibly by reducing the allergic response of asthmatic subjects sensitized to HDM.

Controlled studies of allergic asthma in subjects with single allergy to HDM have shown that specific immunotherapy reduces symptoms⁸ and, in some cases, improves basal airway function.⁵ More recent investigations have demonstrated that sublingual immunotherapy in patients with asthma caused by HDM is effective in reducing symptoms and medication use and might improve respiratory function when compared with placebo treatment.^{19,20} In those studies pharmacologic treatment was not adjusted, and allergen avoidance was not properly implemented. Few studies addressed the question of evaluating the additive benefit of immunotherapy in asthmatic patients treated according to currently accepted pharmacotherapy for asthma.³ The question is relevant because antiasthma drugs are the first choice of treatment in all stages and all types of asthma and are widely available and accessible to patients and physicians. In contrast, it is recommended that specific immunotherapy be prescribed by specialists, and international guidelines indicate that it should be limited to allergic asthma only when environmental avoidance and pharmacologic intervention have failed to control the disease.^{3,21} Our data are consistent with the hypothesis that some mild asthma attacks caused by HDM exposure might be prevented by successful allergen immunotherapy.

A previous controlled trial of immunotherapy for asthma in allergic children with predominant sensitivity to HDM who were receiving appropriate medical care failed to demonstrate significant clinical or functional benefits of immunotherapy over a period of 30 months.⁹ Possible explanations for these results are the inclusion of children with multiple sensitivities and the use of mixtures of allergen extracts for the injections, which reduced the probability of success of allergen desensitization. In our study we extended the evaluation to adults and carefully selected the subjects to maximize the efficacy of immunotherapy.²¹ A significant increase in PEF values and a reduced number of subjects using rescue bronchodilators were detected in the active treatment group. The magnitude of improvement in PEF was similar to that achieved in a large, placebo-controlled long-term study using low doses of budesonide.²²

The proportion of subjects not requiring bronchodilators might be considered proof of asthma control and has been used as an outcome variable to reflect the efficacy of inhaled glucocorticosteroids in a large, long-term controlled study in patients with asthma.²³ In our study the proportion of subjects who did not use bronchodilators was significantly increased in the immunotherapy group, suggesting that immunotherapy was effective. However, the size of the benefit in terms of

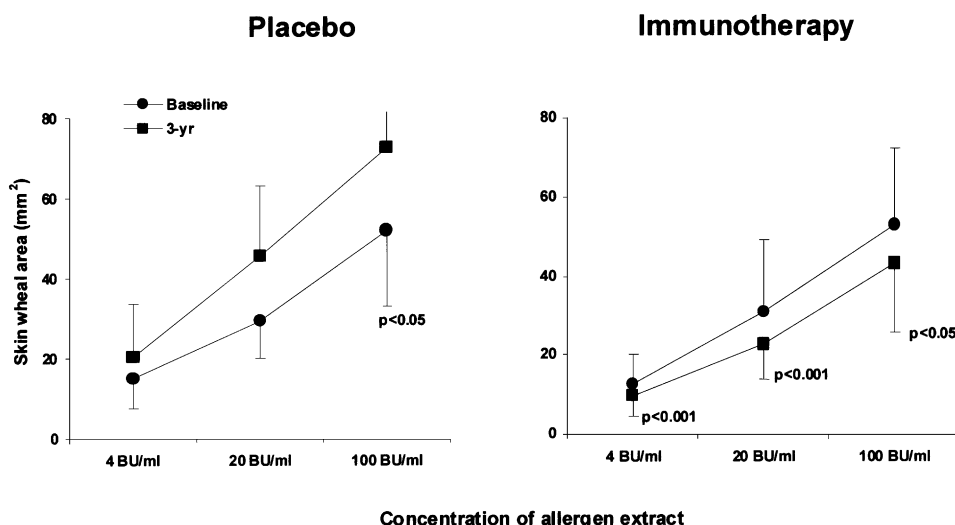


FIG 1. Skin sensitivity to different concentrations of HDM extracts before (*Baseline*) and after 3 years of treatment with placebo or immunotherapy. Data are presented as medians and 25th or 75th percentiles.

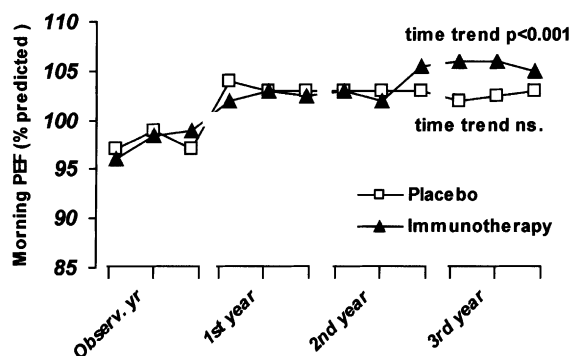


FIG 2. Mean values of morning PEF recorded in the autumn months (September through November) during the observational year and 3 years of treatment with placebo or immunotherapy. *P* values represent the significance of the time trend obtained with a mixed-model ANOVA.

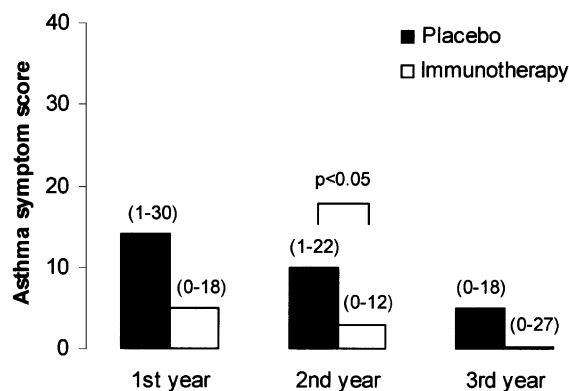


FIG 3. Asthma symptom scores during 3 years of treatment with placebo or immunotherapy. Data represent average monthly scores in autumn months (September through November) and are presented as medians (25th to 75th percentiles in parentheses). The scores of each year were compared between the groups.

reduced antiasthma medication use was small because the average use of inhaled corticosteroids and bronchodilators was not significantly different between the 2 groups. One possible explanation for the marginal clinical relevance of our results could be that the administered dose of allergen was insufficient. For safety reasons, considering that our subjects were asthmatic and that some were children, the lowest amount of relevant antigen recommended by guidelines on immunotherapy was used.²⁴ However, the maintenance dose of the standardized HDM vaccine corresponded to that of the optimal efficacy/safety profile ratio in a dose-titration study,²⁵ and it was achieved in the vast majority of the subjects. Most important, the attendant immunologic effect of immunotherapy, manifested by a significant reduction in skin sensitivity to HDM, was observed. It therefore seems unlikely that an insufficient dose of allergen was administered. In addition, changes in

environmental exposure to HDM caused by looser avoidance measures over time can be ruled out because the levels of HDM antigens in the bedroom dust remained steady throughout the study period.

Another possible explanation for our results is that subjects were overtreated with drugs, thereby masking the effect of immunotherapy. The study design indicated that the investigators, who were blinded to the randomization group, had to consider a reduction of medications when symptom scores and PEF recordings showed acceptable control of asthma. During the study, inhaled steroids were indeed withdrawn, and at the last visit, 33% of subjects were receiving steroids compared with 49% at randomization. Therefore the number of subjects receiving steroids at the end of the study was lower than the number of subjects classified as having moderate asthma at entry.

TABLE III. Proportions of subjects who did not use bronchodilators*

| | No bronchodilator use (%) | |
|--------------------|---------------------------|---------------|
| | Placebo | Immunotherapy |
| Observational year | 26.4 | 22.1 |
| Year 1 | 24.2 | 25.3 |
| Year 2 | 24.2 | 24.1 |
| Year 3 | 25.3 | 28.5 |
| Difference† | -1.1 | +6.4 |
| χ^2 for trend | 1.68‡ | 11.7§ |

*Percentages were calculated from drug records in the autumn months (September through November).

†Year 3 minus percentages in the observational year.

‡Not significant.

§ $P < .01$.

These observations indicate that the reduction of medication was effective, and it was unlikely that subjects were overtreated. It is possible, however, that inclusion in the trial of patients with insufficiently severe disease might have prevented the detection of treatment effects. Subgroup analysis apparently did not confirm this hypothesis because no different outcome was observed in subjects with mild compared with moderate asthma. However, we need to be cautious with this interpretation because the lower number of subjects in subgroups reduces the power of statistics. On the other hand, because of safety concerns, immunotherapy is not indicated when asthma is classified as severe.²¹

A Cochrane review of indices of nonspecific bronchial hyperresponsiveness has confirmed an overall reduction in PD₂₀FEV₁ after immunotherapy⁸ that was detectable relatively shortly (ie, 1 year) after the beginning of treatment with HDM extracts.^{5,26,27} Despite a substantial degree of bronchial hyperresponsiveness in our study population, we did not detect any significant change in PD₂₀FEV₁. Probably allergen avoidance measures and drug treatment during the observational year were sufficient to improve bronchial responsiveness, leaving no room for a further increase in PD₂₀FEV₁.²⁸⁻³⁰

Because the aim of this study was not to evaluate the efficacy of immunotherapy in HDM-sensitive asthmatic patients per se, our results should not be interpreted to mean that immunotherapy is clinically ineffective in this form of asthma. Indeed, several controlled clinical trials have showed that immunotherapy for HDM sensitivity provides protection against the relevant allergen, reduces symptoms, and improves lung function.⁸ The conclusions to be drawn from our study might be that (1) immunotherapy for HDM sensitivity in asthma adds little to adequate pharmacotherapy or that (2) HDM sensitization is not an important trigger for asthma in patients receiving optimal medical care, including allergen avoidance measures, antiasthma drugs, and close medical control. Immunotherapy might be a useful option in subgroups of patients with a lower level of medical care or as an alternative to pharmacotherapy when it is associated with unacceptable side effects. Finally, other properties of

TABLE IV. Bronchial responsiveness to methacholine (PD₂₀FEV₁)

| | PD ₂₀ FEV ₁ (μg) | |
|--------------------|----------------------------------------|---------------|
| | Placebo | Immunotherapy |
| Observational year | 95 (44-203) | 158 (91-274) |
| Year 1 | 144 (69-300) | 198 (119-331) |
| Year 2 | 127 (60-267) | 226 (129-394) |
| Year 3 | 175 (101-305) | 183 (104-322) |
| Time trend | $P = NS$ | $P = NS$ |

Data are presented as geometric mean (95% CI). No significant differences between groups were detected at any time point.

NS, Not significant.

specific immunotherapy have to be considered, such as its long-lasting effects^{31,32} and the capacity to prevent progression of allergic rhinitis to asthma.³³

We thank Dr Paola Puccinelli from ALK-Abellò for the invaluable support in designing and performing the study. We thank Giovanna Fulgeri for secretarial assistance and Fiorenza Griggio, Adriano Battan, Paola Bortolami, Fabrizio Bortolami, and Luigi Zedda for technical assistance.

The members of the Regione Veneto Study Group on "Effect of immunotherapy in allergic asthma": L. Andri, L. Berardino, P. Bernardis, V. Calvo, O. Cappellato, S. Crescioli, M. Crivellaro, A. De Rossi, B. Di Campli, C. Gemignani, S. Macaluso, G. Marcer, G. Moro, L. Murer, G. Piacentini, I. Piazza, G. Senna, P. Serena, A. Sirena, C. Sivini, and E. Volpato.

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