

Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study)

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Asthma, rhinitis,
other respiratory
diseases

Background: Children with allergic rhinitis are likely to develop asthma.

Objective: The purpose of this investigation was to determine whether specific immunotherapy can prevent the development of asthma and reduce bronchial hyperresponsiveness in children with seasonal allergic rhinoconjunctivitis.

Methods: From 6 pediatric allergy centers, 205 children aged 6 to 14 years (mean age, 10.7 years) with grass and/or birch pollen allergy but without any other clinically important allergy were randomized either to receive specific immunotherapy for 3 years or to an open control group. All subjects had moderate to severe hay fever symptoms, but at inclusion none reported asthma with need of daily treatment. Symptomatic treatment was limited to loratadine, levocabastine, sodium cromoglycate, and nasal budesonide. Asthma was evaluated clinically and by peak flow. Methacholine bronchial provocation tests were carried out during the season(s) and during the winter.

Results: Before the start of immunotherapy, 20% of the children had mild asthma symptoms during the pollen season(s). Among those without asthma, the actively treated children had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis (odds ratio, 2.52; $P < .05$). Methacholine bronchial provocation test results improved significant in the active group ($P < .05$).

Conclusion: Immunotherapy can reduce the development of asthma in children with seasonal rhinoconjunctivitis. (*J Allergy Clin Immunol* 2002;109:251-6.)

Key words: Prevention, specific immunotherapy, bronchial hyperresponsiveness, asthma, rhinitis

A link between hay fever and asthma is evident,^{1,2} and more than 70% of asthma patients report nasal symptoms.³ Approximately 20% of all hay fever patients develop asthma later in life.^{4,5} It has been found that 11% to 73% of hay fever patients show bronchial hyperresponsiveness (BHR) outside the pollen season⁶⁻⁹ and that up to approximately 50% of such patients show BHR during the season.^{9,10} Rhinitis frequently precedes the onset of asthma,^{11,12} and patients with allergic rhinitis who also have BHR are more likely to develop asthma.^{6,10,13}

The clinical efficacy of specific immunotherapy (SIT) treatment for pollen allergy has been confirmed in several studies.¹⁴⁻¹⁸ One investigation showed that none of the patients who initially had only hay fever developed asthma during the total study period of 8 years,¹⁹ and in a study of oral immunotherapy in children with pollinosis, 31% of those in the placebo group, in comparison with none in the active group, developed asthma.²⁰ The only long-term investigation of the preventive potential of SIT showed a significant reduction in the number of children who developed asthma.²¹

In birch pollen-allergic patients with mild to moderate asthma, SIT can reduce BHR.¹⁵ Although the process is not understood in detail, SIT has a profound influence on the immune system, and the clinical changes achieved appear to persist for many years.²²

The primary aim of the present study was to investigate whether SIT with birch and/or timothy pollen allergen extracts in children with hay fever could reduce the risk of developing asthma and/or influence BHR.

METHODS

Patients

A total of 208 children aged 6 to 14 years from European 6 pediatric centers were included in the study; of these, 205 were randomized after a baseline season (season 0; Table I). Each of the chil-

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TABLE I. Patient demographic data at inclusion

	All included	No asthma	Asthma*
No. of patients	208 (205)†	163	42
Age (y): mean (range)	10.7 (6-15)	10.7 (6-15)	10.6 (6-14)
Sex: male/female	138/70 (137/68)†	108/55	29/13
Years with hay fever: mean (range)	4.7 (1-15)‡ N = 171	4.6 (1-15)‡ N = 137	4.9 (1-9)‡ N = 34
Methacholine PC ₂₀ : mean (range)	10.8 (0.03-16)	12.2 (0.16-16)	5.1 (0.03-16)
Control/SIT for 3 y	94/97	72/79	22/18

*Mild seasonal asthma during the first season before randomization.

†Three patients dropped out before baseline monitoring (season 0).

‡Only data for patients with reliable information have been included.

Abbreviations used

BHR: Bronchial hyperresponsiveness

MBPT: Methacholine bronchial provocation test

SIT: Specific immunotherapy

dren had a clinical history of rhinoconjunctivitis caused by allergy to birch and/or grass pollen. Further inclusion criteria were positive skin prick test and conjunctival provocation test results. A skin prick test result was considered positive if the mean weal diameter with Soluprick SQ 10 HEP (ALK-Abelló) was ≥ 3 mm,²³ and a conjunctival provocation test result was considered positive if the threshold concentration with Aquagen SQ (ALK-Abelló) was $\leq 100,000$ SQ units/mL.²⁴ Patients were excluded from the study if they had symptoms consistent with positive skin test results to any allergen other than grass and/or birch, if they had undergone previous SIT treatment, or if they had asthma with need of daily medication.

The children and their parents gave informed consent according to the standards of the Helsinki declaration. Ethical committees approved the study in the respective countries.

Treatment

The flow chart for the study is presented as Fig 1. Patients were included and treatment was initiated during the period 1992 through 1994. After the children were stratified on the basis of (a) bronchial responsiveness to methacholine during season 0, (b) age, (c) sex, and (d) years with pollinosis according to history, they were randomized into 2 groups. To reduce the influence of differences in pollen exposure, randomizations were performed center for center. Both groups were allowed to take symptomatic medication, but this was limited to (a) loratadine tablets (5-10 mg/day), (b) nasal levocabastine, and/or (c) ocular sodium cromoglycate. If necessary, nasal budesonide (up to 100 μ g/day in each nostril) was allowed. In case of asthmatic symptoms, short-acting β_2 -agonists were prescribed. When needed, inhaled corticosteroids could be introduced. One group was treated with SIT for 3 years; the other group served as an open control group. Because SIT was given for 3 years and the study was not a basic efficacy study, it was regarded as unethical to include subcutaneous placebo treatment.

SIT was initiated after season 0 with characterized and standardized allergen extracts of grass pollen (*Phleum pratense*) and/or birch pollen (*Betula verrucosa*). Dosing was performed with depot extracts (Alutard SQ, ALK-Abelló), with weekly injections over 15-20 weeks, or as rush immunotherapy with aqueous extracts (Aquagen SQ, ALK-Abelló). Maintenance injections with depot preparations were given every 6 weeks (± 2 weeks) for a total period of 3 years. The contents of major allergen per maintenance injection

(Alutard SQ 100,000 SQ units/mL) corresponded to 20 μ g of Phl p 5 (grass) and 12 μ g of Bet v 1 (birch).

Skin prick testing

Skin tests were performed on the flexure aspect of the forearm in duplicate before the start of SIT. The following allergen extracts were used: timothy, birch, mugwort, dog, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, and *Alternaria alternata* (Soluprick SQ, 10 HEP/molds 1/20 w/v, ALK-Abelló).²³

Conjunctival provocation testing

Conjunctival provocation tests were performed outside the pollen season (always at the same time of year), before the start of immunotherapy, and after 1, 2, and 3 years. Half ^{10} log increments at concentrations from 100 to 1,000,000 SQ units/mL were used (Aquagen SQ, ALK-Abelló).²⁴

Methacholine bronchial provocation testing and peak flow

Methacholine bronchial provocation tests (MBPTs) were performed during season 0 before randomization, in the relevant pollen season(s), and during the winter. Tests were performed through use of the reservoir method described by Matthys et al.²⁵ This method involves the use of a high-quality nebulizer system (Pari Provocation Test 2) combined with a 10-L storage bag; the method allows for standardized pulmonary aerosol deposition at saturated ambient temperature and pressure conditions. First, a 0.9 molar NaCl solution was nebulized and inhaled; then, test solutions of 0.5, 1, 2, 4, 8, and 16 mg/mL methacholine were nebulized and inhaled. In cases of suspected asthma, the tests were initiated with lower concentrations. FEV₁ was measured 3 times before exposure and 3 minutes after each inhalation; the highest value was recorded. The tests were stopped either after inhalation of the highest concentration of methacholine (16 mg/mL) or at the concentration giving a $\geq 20\%$ decrease in FEV₁ in relation to baseline. The PC₂₀ was estimated by linear interpolation of the 2 last (log-transformed) concentrations tested. In each center, the same devices for measuring FEV₁ were used on all test occasions. Identical dilution instructions for methacholine were used at each center.

Morning and evening peak flow was monitored at home during the season(s) and for 1 month each winter throughout the study.

Visual analog scale

Symptoms of conjunctivitis, rhinitis, and asthma in comparison with pretreatment symptoms were evaluated on a 100-mm visual analog scale (VAS) after every season.

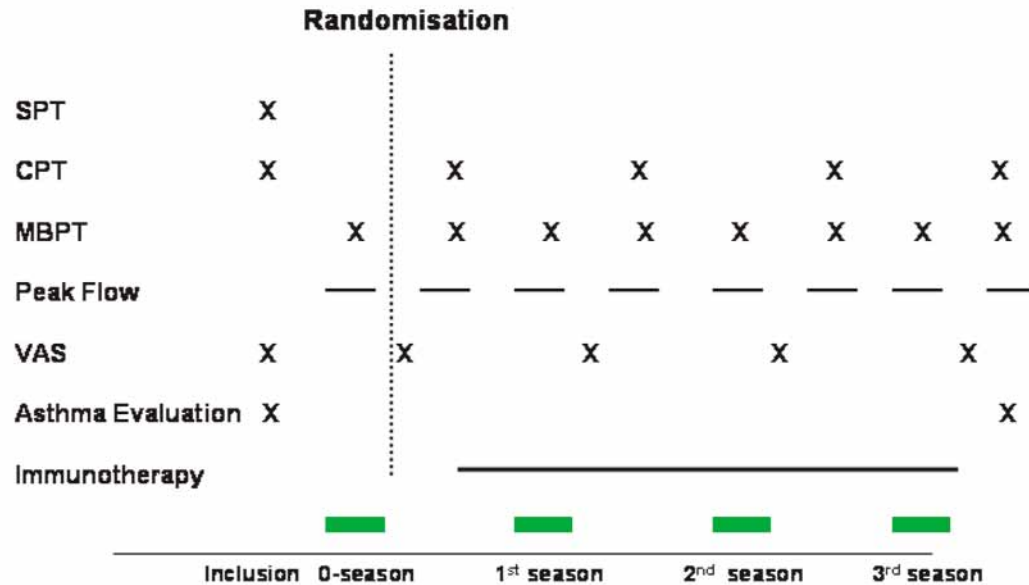


FIG 1. Flow chart of the study.

Asthma diagnosis

Asthma was defined as recurrence of at least 2 of the following 3 symptoms within the previous 12 months:

- Cough
- Wheeze
- Shortness of breath.

Further demands for the conclusive diagnosis of asthma were that the symptoms be triggered not only by infections and that the patients respond to treatment with β_2 -agonists. The clinical diagnosis was based only on the appearance of repeated symptoms and was independent of the level of hyperresponsiveness.

Statistical methods

Changes from baseline of log-transformed values of conjunctival provocation test results were analyzed within groups by Wilcoxon sign rank testing and between groups by Wilcoxon rank sum testing. Of the 41 children allergic to both birch and grasses, 25 performed only 1 symptom score VAS because of exposure overlap between the seasons; these score results have been included twice to represent both seasons. Changes from baseline of VAS scores of conjunctivitis and rhinitis were analyzed within and between groups through use of *t* testing. Changes from baseline of VAS scores of asthma were analyzed within groups by sign testing and between groups by Wilcoxon rank sum testing.

Changes from baseline of logarithmic transformed values of MBPT results were analyzed within groups by Wilcoxon sign rank testing and between groups by Wilcoxon rank sum testing. MBPT values were transformed into a 6-step ordinal scale defined by the groupings ≤ 0.032 , ≤ 0.125 , ≤ 0.5 , ≤ 2.0 , ≤ 8.0 , ≤ 32.0 , and changes from baseline of scale-transformed MBPT results were analyzed within groups by Wilcoxon sign rank testing and between groups by Wilcoxon rank sum testing.

Because of the large range and variability with regard to BHR, there was a risk of underestimating differences between the groups. We decided to calculate the odds ratio for improvement; by this method, can one get an impression of the difference in improvement between groups. An exploratory analysis was done in an ordinal-scaled, repeated-measure model through use of the Generalised Estimation Equations.²⁶

Peak flow data from each patient were included for statistical analysis if complete data were available from at least 2 consecutive weeks during seasonal exposure as well as during the winter. Between-groups comparisons of peak flow were conducted by means of Wilcoxon rank sums testing. The treatment groups were compared with respect to the mean and difference between daily measures of evening and morning peak expiratory flow.

Clinically diagnosed asthma was analyzed at each center through use of the Fischer exact test, and homogeneity of odds ratios between centers was tested through use of the Zelen exact test. We calculated the mean odds ratio of clinically diagnosed asthma in accordance with the International Conference on Harmonisation E9 guidelines,²⁷ weighing centers equally, weighing by the precision of the odds ratios, and using a mixed logistic model with random-center and treatment-by-center effects.

The statistical analysis was carried out through use of SAS version 6.12, SAS version 7.0, and StatXact version 3.0. Two-sided tests and a test significance level of 5% were used.

RESULTS

Forty-three patients were allergic to birch, 124 were allergic to grass, and 41 were allergic to both birch and grass. Before SIT, despite negative histories of asthma with need of daily medication at screening, 40 children (20%) were identified as having mild asthma. These mild seasonal asthmatic symptoms would probably not even now have been identified if the patients had not been enrolled in the study. According to the skin prick test results, the average number of sensitivities other than to birch and/or timothy for the whole group of patients was 1.6. Twenty-eight patients had more than 3 other sensitivities, whereas 56 had no other sensitivities. Eight controls and 6 active patients dropped out during the 3-year period.

In contrast with what was seen in the SIT group, no statistically significant reduction in conjunctival sensitivity was seen in the control group ($P < .001$). The difference in favor of the SIT group compared to the control group was significant ($P < .001$).

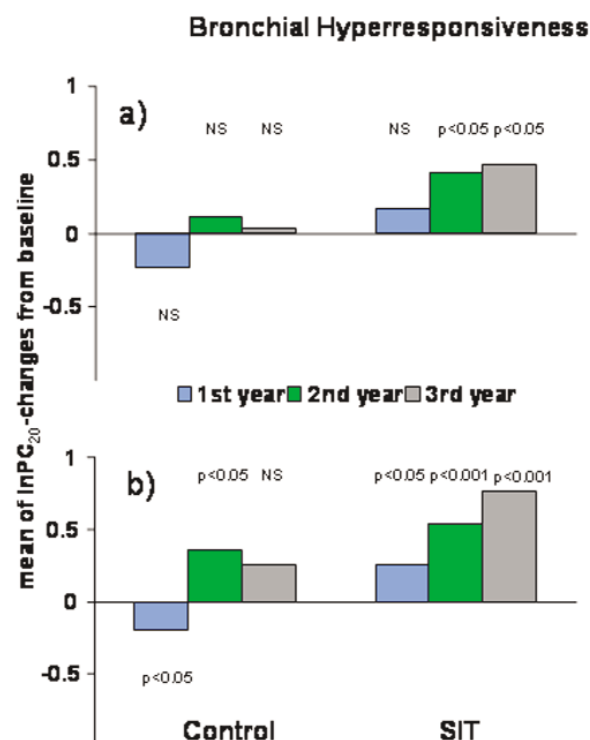


FIG 2. Development of BHR (methacholine challenge test) within each group measured as natural logarithm of PC_{20} change from baseline (a) in the season of pollen exposure and (b) during the winter.

TABLE II. Mean odds ratios for improvement of bronchial hyperresponsiveness (methacholine challenge test): immunotherapy group vs controls

	Year one	Year two	Year 3
Season			
Odds ratio	1.70	1.40	1.43
95% CI	1.0-2.9	0.8-2.6	0.8-2.7
No. of patients	201	191	168
Winter			
Odds ratio	2.34	1.39	2.78
95% CI	1.3-4.2	0.7-2.7	1.2-6.3
No. of patients	191	186	106

PC_{20} values are transformed to a 6-step ordinal scale defined by the following groupings: ≤ 0.032 , ≤ 0.125 , ≤ 0.5 , ≤ 2.0 , ≤ 8.0 , ≤ 32.0 . Changes from baseline were analyzed between groups by Wilcoxon rank sum testing.

BHR with $PC_{20} < 2$ mg/mL was found during the first birch season in 48%, during the first grass season in 37%, and during the first winter in 33% of the children. Before the start of SIT, 25% did not respond to the highest test concentration during the pollen season and 34% did not respond during the winter. Mean (range) seasonal PC_{20} values for the SIT and control groups, respectively, were 10.4 (32-0.13) and 11.1 (32-0.03) mg/mL at baseline and 14.9 (32-0.15) and 12.2 (32-0.11) mg/mL at the end of the study. The corresponding winter PC_{20} values were 12.8 (32-0.14) and 13.5 (32-0.07) mg/mL at baseline and

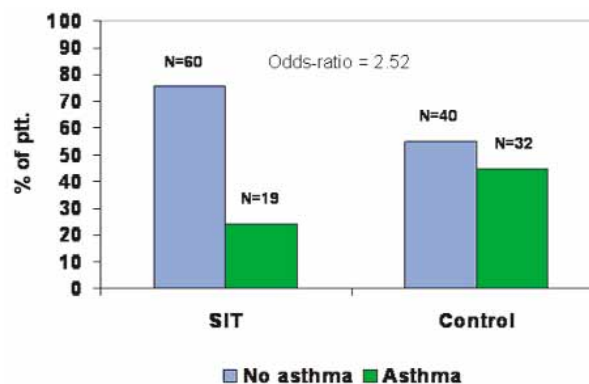


FIG 3. The percentage of children after 3 years of immunotherapy with and without asthma among those without asthma before treatment (N = 151). The absolute numbers of children are shown above the bars.

17.2 (32-0.22) and 14.3 (32-0.10) mg/mL. During seasonal exposure, as well as during the winter, the BHR, measured as change from baseline (season 0), improved significantly in the SIT group after 2 and 3 years of treatment (Fig 2, A and B). The odds ratio for improvement of BHR was significantly in favor of the SIT group after 1 year during seasonal exposure and after 1 and 3 years outside the season (Table II). (The 3-year winter challenge was performed in only 4 centers because of the national regulatory situation in one of the centers and technical problems in another.)

The means of morning and evening peak flow measurements are illustrated in Table III.

The children were well matched for lung function at inclusion but represented a wide range of values, as could be well expected in this patient population. Peak flow increased during the study period because of normal growth of the children, and we could not see any significant differences between the SIT and control patients.

Improvements were seen in the VAS score for conjunctivitis for both groups. This improvement was significantly to the advantage of the SIT group after 1, 2, and 3 years of treatment ($P < .001$, $P < .001$, and $P < .05$, respectively). The rhinitis VAS symptom score showed a significant improvement in the SIT group in comparison with the control group after 2 years ($P < .05$) and 3 years ($P < .01$) of treatment. Twenty-five children in the control group and 21 children in the active group had been prescribed nasal steroids. Among those with new asthma after 3 years, 53% (17/32) of the controls and 47% (9/19) of those in the SIT group used nasal steroids, whereas among those without asthma 20% (8/40) of the controls and 20% (12/60) of those in the SIT group used nasal steroids.

Two of the 40 children with asthma at randomization were free of asthma after 3 years. Children without asthma before the start of SIT (n = 151) were analyzed for the development of asthma after the 3-year period. The final outcome of asthma development for all centers, according to our definition, showed an odds ratio of 2.52 (1.3-

TABLE III. Averages of morning/evening peak flow values

	Baseline	1st year	2nd year	3rd year
SIT				
Season	345 (203-568)	379 (219-592)	416 (270-646)	446 (302-659)
Winter	375 (238-750)	406 (267-601)	434 (278-672)	495 (282-615)
Control				
Season	343 (192-571)	377 (216-636)	417 (242-698)	447 (275-701)
Winter	367 (200-604)	398 (237-645)	434 (252-697)	467 (288-690)

PEF data from each patient were included for statistical analysis if complete data were available from at least 2 consecutive weeks during seasonal exposure as well as during the winter.

TABLE IV. Absolute numbers of children among those without asthma before immunotherapy (N = 151) from individual centers with and without asthma 3 years after initiation of treatment

Group	Center 1		Center 2		Center 3		Center 4		Center 5		Center 6	
	SIT	Control	SIT	Control	SIT	Control	SIT	Control	SIT	Control	SIT	Control
No asthma	5	6	0	6	22	11	13	8	15	7	5	2
Asthma	2	0	7	3	1	2	5	10	3	14	1	3
Odds ratio	0		0		4.0		3.25		10.0		7.5	
P value	.46		.01		.54		.18		.003		.24	

Center 2 is inhomogeneous with the other 5 centers.

5.1; $P < .05$) in favor of the hypothesis that SIT can prevent the development of asthma in children with pollinosis (Fig 3). When calculating a common odds ratio, we found that each of 4 centers had a positive odds ratio for the prevention of asthma (3.25-10) and that 2 centers had an odds ratio of less than 1 (Table IV). The hypothesis that all centers could be characterized by a common odds ratio was rejected ($P < .001$).

At one center (16 patients), significantly more children in the SIT group developed asthma ($P < .01$). In this center, hyperventilation of cold air testing was performed in all children for other investigational purposes. Because this is a very sensitive test, it would likely bias the data, inasmuch as more children in this center have had an experience of asthma. There were no differences in inclusion criteria among centers, and the other 5 centers showed homogeneity. The estimated odds ratio for the 5 homogeneous centers was 3.9 (1.72-9.15; $P < .001$).

The VAS asthma scores after the season(s) after 1, 2, and 3 years increased in comparison with baseline values in both groups, but less so in the SIT group; the difference was significant for birch pollen-allergic children ($P < .05$).

Significantly more children ($P < .05$) in the control group reported increased asthma symptoms after 2 years (38 controls/25 active) and 3 years (40 controls/29 active). The mean measures at baseline for asthma score were 5.0 and 5.4 in the active and control groups, respectively. After 3 years, the control group, in contrast to the active group, had a significant increase to 11.9 ($P < .01$). In general, the VAS scores for asthma were low, but they represented a wide range (0-97.5).

DISCUSSION

This study shows that SIT in children with rhinoconjunctivitis without asthma reduced the risk for later

development of asthma. Because SIT for hay fever can prevent allergic asthma, it appears that allergic rhinoconjunctivitis and allergic asthma are different manifestations of the same disease. Children with hay fever but without asthma with need of daily medication were selected for the study. When they were initially challenged with methacholine during seasonal exposure, we found a very high degree of seasonal BHR, indicating a link between the nose and the lung.

The main endpoint was the development of asthma. Thus it was essential to keep the definition of asthma in the study precise. The recurrence of 3 core symptoms was chosen in accordance with a later position paper (of the Global Initiative For Asthma).²⁸ The use of symptoms appears to have a better predictive value than the use of MBPT.^{29,30} Symptoms alone, even if recurrent, are not diagnostic for asthma; rather, the relief of the symptoms by bronchodilator therapy is.²⁸ It is important to stress that in this study asthma was defined in a qualitative way and that all asthma was mild to moderate. The use of nasal steroids was lowest in those children who did not develop asthma. It is therefore unlikely that nasal steroid treatment has added to the preventive effect on development of asthma.

In one center, the results regarding the clinical diagnosis of asthma are contradictory. The analysis of this multicenter study is similar to the challenge that the statistician meets in meta-analyses of different investigations. Inasmuch as these children also participated in another study, it might be argued that we should not have included them in our analysis. The numbers in the particular center were small and did not impact the overall findings for the 6 centers studied. Despite the lack of homogeneity for all centers, the clear difference in favor of the group of children treated with SIT in comparison with the control group shows that SIT has the potential to reduce the risk of development of asthma.

It has been suggested that patients with allergic rhinitis and BHR are those most likely to develop asthma.^{6,10,13} However, some investigations indicate that this is not the case. Children with rhinitis without diagnosed asthma often have BHR, but this could not predict the risk for later asthma, according to one of these studies.³¹ It is possible that the high prevalence of BHR in our nonasthmatic patient group is a sign of lower airway disease.

The reduction of BHR as measured by MBPTs was more pronounced in the group treated with SIT, as illustrated in Fig 2. The positive odds ratio in favor of the SIT group was not significant during the season after 2 and 3 years of treatment. As shown in Table II, a reduced number of children were tested in the third year. The majority of the missing children belonged to the center where SIT had the highest protection for development of asthma—ie, center 5 (Table IV). Thus it could be suspected that the difference in changes of BHR between the groups in the third year would have been even more pronounced if all patients had been tested.

That SIT is acting by influencing basic immunologic mechanisms is documented in several studies.^{15,32,33} It is plausible that if immunotherapy improves the symptoms from one part of the airways—ie, the nose—it also has the potential to give the same immunologic response in another part—ie, the lungs. That SIT has the potential to change the natural course of the allergic disease by prevention was first suggested by Johnstone and Dutton²¹; this was later confirmed.^{19,34}

Our study demonstrates that a 3-year course of SIT in children with allergic rhinoconjunctivitis significantly reduces the risk of developing clinical asthma and improves BHR.

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