

Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma

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Background: Few studies have investigated the use of specific immunotherapy (SIT) for childhood seasonal allergic asthma. **Objective:** We sought to examine the efficacy and safety of SIT with Alutard SQ grass pollen (*Phleum pratense* Alutard SQ; ALK-Abelló, Hørsholm, Denmark) in children with seasonal allergic asthma.

Methods: A randomized, double-blind, placebo-controlled study assessing the efficacy of grass pollen SIT over 2 pollen seasons was performed. Children (3-16 years) with a history of seasonal allergic asthma sensitized to grass pollen (*P pratense*) and requiring at least 200 µg of inhaled beclomethasone equivalent per day were enrolled. Subjects with symptomatic asthma or rhinoconjunctivitis outside the grass pollen season were excluded. The primary outcome measure was a combined asthma symptom-medication score during the second pollen season. Secondary outcome measures included end-point titration skin prick testing and conjunctival and bronchial provocation testing to allergen, sputum eosinophilia, exhaled nitric oxide, and adverse events.

Results: Thirty-nine subjects were enrolled. Thirty-five subjects provided data for analysis. The use of SIT was associated with a substantial reduction in asthma symptom-medication score compared with that after placebo ($P = .04$). There were also significant reductions in cutaneous ($P = .002$), conjunctival ($P = .02$), and bronchial ($P = .01$) reactivity to allergen after SIT compared with that after placebo. The 2 groups had similar levels of airway inflammation, despite a trend toward less inhaled steroid use in the active group. No serious adverse events were reported, and no subjects withdrew because of adverse events.

Conclusion: The study has shown that SIT is effective and well tolerated in children with seasonal allergic asthma to grass pollen. (J Allergy Clin Immunol 2006;117:263-8.)

Key words: Seasonal allergic asthma, children, immunotherapy

Abbreviations used

IQR: Interquartile range
SIT: Specific immunotherapy
SQ-U: Standardized quality units

There is considerable evidence for the efficacy and safety of specific immunotherapy (SIT) in children and adults with allergic rhinoconjunctivitis.¹⁻³ A recent systematic review suggests that immunotherapy is effective in adult allergic asthma.⁴ However, some trials have failed to provide clear evidence. This might partly be due to the study design, insufficient number of patients, inappropriate subjects, or insufficient quantity of allergen used.⁴ Additionally, there has been a concern about the number of adverse effects seen when asthmatic patients are treated with SIT.⁵ In particular, there are minimal pediatric data on the efficacy and safety of SIT in grass pollen-induced asthma. In adults SIT has been shown to reduce the need for corticosteroid therapy and to modify the natural history of allergic rhinitis.² If these effects are also seen with childhood allergic asthma, SIT has the potential to have a major role in the management of this disease.

Children and teenagers with seasonal allergic asthma form an ideal group to assess the efficacy of immunotherapy for allergic asthma. Symptoms are almost completely confined to a defined pollen season. Outside this period, they have normal lung function without a requirement for inhaled corticosteroids. Additionally, immunotherapy might be expected to benefit coexisting allergic rhinoconjunctivitis.¹⁻³ We studied the clinical efficacy and safety of SIT in children with seasonal allergic asthma using an asthma symptom-medication score as the primary outcome measure. We also measured changes in specific allergen reactivity and airway inflammation.

METHODS

Design

Children and teenagers with seasonal allergic asthma were randomized to receive SIT or placebo over 2 successive pollen seasons. The study was a single-center, randomized, double-blind, placebo-controlled study over 2 successive pollen seasons. The primary end point was the asthma symptom-medication score during the second pollen season. Good clinical practice was applied,⁶ the

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TABLE I. Details of subjects

	Active group	Placebo group
All subjects	18 (100.0%)	17 (100.0%)
Female subjects	5 (27.8%)	5 (29.4%)
Ethnic origin		
White/English/Scottish/Welsh	12 (66.7%)	13 (76.5%)
Black African/Caribbean/Other	2 (11.1%)	1 (5.9%)
Indian subcontinent	4 (22.2%)	1 (11.8%)
White other	0 (0.0%)	1 (5.9%)
Mean age (SD)	9.2 (4.4)	10.6 (2.9)
Mean weight (SD)	37.3 (22.0)	39.3 (12.1)
Mean height (SD)	134 (27.2)	139 (17.8)
Summer asthma		
Mild symptoms	0 (0.0%)	0 (0.0%)
Moderate symptoms	15 (83.3%)	15 (88.2%)
Severe symptoms	3 (16.7%)	2 (11.8%)
Summer rhinoconjunctivitis		
Mild symptoms	3 (16.7%)	0 (0.0%)
Moderate symptoms	15 (83.3%)	14 (82.4%)
Severe symptoms	0 (0.0%)	3 (17.6%)
Atopic dermatitis	9 (50.0%)	5 (29.4%)
Symptoms on exposure to tree pollen	2 (11.1%)	0 (0.0%)
Symptoms on exposure to house dust mite	5 (27.8%)	2 (11.8%)
Symptoms on exposure to animal hair and dander	8 (44.4%)	6 (35.3%)
Median (IQR) daily inhaled beclomethasone (or equivalent) dosage during summer before entering study	400 (400-400)	400 (200-400)

Mild symptoms had only a minimal effect on daily life, moderate symptoms were defined as having a significant effect on at least 50% of days, and severe symptoms have a major effect on life with daily symptoms. Subjects only had mild symptoms on exposure to tree pollen or house dust mite.

study was approved by the Local Research Ethics Committee of St Mary's, and informed consent was obtained from families.

Subjects

Subjects aged 3 to 16 years were recruited from the chest and allergy clinic at St Mary's, through local pediatricians, or through an advertisement placed in the local press. All had a clinical history of grass pollen-induced asthma⁷ requiring at least 200 µg of inhaled beclomethasone (or equivalent) daily. Asthma severity was classified according to its effect on each subject's life (Table I). All subjects had a positive skin prick test response (wheal ≥ 3 mm, Soluprick SQ, 10 histamine equivalent prick *Phleum pratense*; ALK-Abelló, Hørsholm, Denmark), a positive specific IgE level (>0.7 IU/mL; Pharmacia CAP, Uppsala Sweden), and a positive conjunctival provocation test result (described below; $\leq 32,000$ standardized quality units [SQ-U]/mL Aquagen SQ *P pratense*; ALK-Abelló). Exclusion criteria were as follows: previous grass pollen immunotherapy, perennial asthma requiring inhaled corticosteroids, significant perennial allergic rhinitis, or sensitization to a pet present in the household. This allowed recruitment of a group of children with allergic asthma and rhinoconjunctivitis symptoms that were almost entirely caused by grass pollen. At enrollment, skin prick tests were performed with a standard panel, including most common inhalant allergens (*P pratense*, cat, dog, horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Alternaria alternata* (Soluprick SQ)).⁸

TABLE II. Immunotherapy up dosing schedule¹

Visit	Concentration (SQ-U/mL)	Dose (SQ-U)
1	100	10
	1000	100
	10,000	1000
2	10,000	2000
	10,000	4000
3	10,000	6000
	100,000	10,000
4	100,000	10,000
	100,000	20,000
5	100,000	30,000
	100,000	30,000
6	100,000	50,000
	100,000	50,000
7	100,000	100,000
8	100,000	100,000

Injections were given at 30- to 60-minute intervals. There was a 1-week interval between visits 1 to 6, 2 weeks for visits 6 to 7, 4 weeks for visits 7 to 8, and 6 (± 2) weeks for the maintenance injections.

Immunotherapy

For grass pollen SIT, Alutard SQ *P pratense* (ALK-Abelló) was used. This is an alum-adsorbed preparation of pollen from *P pratense* with a recommended dose of 100,000 SQ-U. This corresponds to 20 µg of major allergen (Phl p 5). It was expected that the immunotherapy preparation would cause local symptoms. Therefore a placebo containing histamine was used to maintain blinding (Alutard diluent, histamine dihydrochloride 0.00001, 0.0001, 0.001, and 0.01 mg/mL). Active and placebo medications were identical in color and viscosity.

To minimize any local discomfort, topical local anesthetic cream (EMLA; Astra Pharmaceuticals, Kings Langley, United Kingdom) was applied, and loratidine (10 mg, 5 mg if <30 kg) was administered before injection.⁹ SIT was performed in an outpatient setting with the dosing schedule shown in Table II.¹ All patients were pretreated with loratidine and topical anesthetic creams, and subjects were observed for 60 minutes after each injection. Standard guidelines were used in the case of intercurrent illness or adverse reactions.^{10,11} Randomization was performed in blocks, with subjects stratified into moderate or high doses of inhaled corticosteroids (≤ 400 or >400 µg daily during previous pollen season) by using random number-generating software.

Rescue medication during the pollen season

During the grass pollen season, subjects were allowed to use rescue medications for symptoms of hay fever (cromoglycate eye drops, azelastine nasal spray, loratidine, or mometasone nasal spray) and asthma (inhaled terbutaline or salbutamol, budesonide through a nebulizer, salmeterol, or prednisolone). They were treated in a step-up/step-down manner according to clinical symptoms, as defined by a protocol. Asthma medications were assigned scores (see additional text in the Online Repository at www.jacionline.org) according to their relative clinical efficacies.

Outcome measures

Asthma diary. Subjects completed a symptom-medication diary during each grass pollen season. The following asthma symptoms were recorded: wheezing, coughing, shortness of breath, tight chest, and breathing problems while exercising. Each symptom was scored as 0 (no symptoms) to 3 (severe symptoms).

Lung function. Lung function was recorded twice a day during the pollen season by using small, portable, electronic personal

spirometers (Ferraris, Bainham, United Kingdom). Each subject's predicted FEV₁ was defined as the second highest value when the subject was well before the grass pollen season.

Cutaneous, conjunctival, and bronchial allergen reactivity. End-point titration to skin prick tests was performed with increasing concentrations of *P pratense* Soluprick SQ at baseline and after each pollen season. Conjunctival provocation testing with *P pratense* Aquagen SQ was undertaken at baseline and after each pollen season. Bronchial provocation testing was performed with increasing concentrations of allergen at baseline and after the second pollen season. Full details are given in the Online Repository at www.jacionline.org.

Exhaled nitric oxide. Exhaled nitric oxide was measured every 4 weeks during the second pollen season by using a single expiratory breath method with a chemiluminescence analyser (Logan Research LR2500, Rochester, United Kingdom), according to European Respiratory Society guidelines.¹² Exhaled nitric oxide values for individual subjects were standardized by expressing them as a proportion of the subject's average preseason level.¹³ Full details are given in the Online Repository at www.jacionline.org.

Sputum eosinophils. Subjects attempted to cough up sputum after inhaling 3.5% nebulized saline for 5 minutes during the peak of the second pollen season.¹⁴ A cell preparation was prepared with dithiothreitol (Sigma-Aldrich, Poole, United Kingdom), and cytospin preparations were prepared (see the Online Repository at www.jacionline.org for full details). Differential cell counts were determined by 2 trained laboratory scientists.

Pollen count

Daily atmospheric pollen counts for the Northwest London area were measured with a Burkard 7-day volumetric spore trap (National Pollen Research Unit, University of Worcester, United Kingdom) in Northwest London. The pollen seasons were defined as dates between which counts were regularly greater than 10 grains per cubic meter; these were determined as May 31 through July 26, 2000, and May 29 through July 26, 2001, before the study was unblinded.

Analysis

The primary outcome measure was the asthma symptom-medication score during the second pollen season. The combined symptom-medication score was generated from the weighted sum of the mean asthma symptom and medication scores, each weighted by their inverse variance. The analysis included all randomized subjects with diary data available. Missing data were replaced by data derived from the outcome of an ANOVA that included the 2 factors of subject and date on all available scores from within the pollen season. The secondary end points were the asthma symptom-medication scores during the first pollen season; cutaneous, conjunctival, and bronchial allergen reactivity; lung function; exhaled nitric oxide; sputum eosinophilia; and adverse effects. Throughout the analyses, a significance level of 5% was used. The sample size calculation was based on a 5% significance level, an expected difference of 20%, and an SD of 20%. A power of 90% would then require a total of 42 subjects. Analyses were undertaken with SAS version 8e (SAS Institute, Inc, Cary, NC) and Stata version 6 (Statacorp, Houston, Tex).

RESULTS

Subjects

Thirty-nine subjects were enrolled in the study, and 37 reached the maintenance dosage (Fig 1). Of these 37 subjects, one subject withdrew from the study for personal reasons before the first pollen season, and one subject was withdrawn from the study when perennial asthma

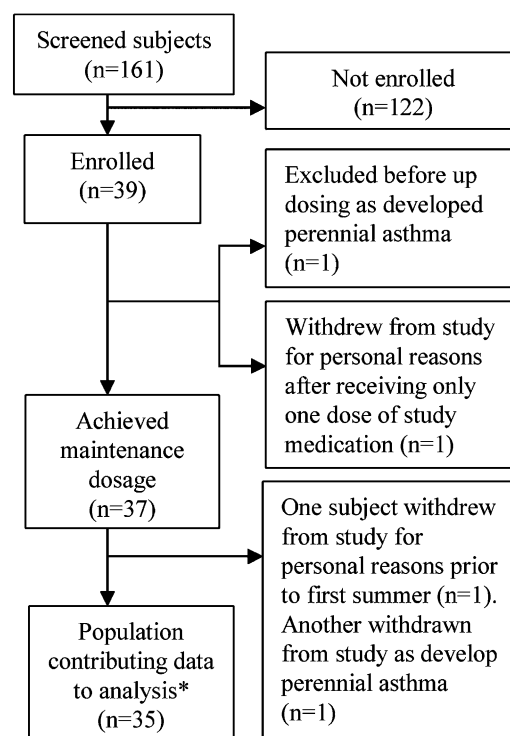


FIG 1. Details of all subjects involved in the study. Two of the 35 subjects contributing data to the analysis (marked with asterisk) stopped immunotherapy just before the second pollen season, one because of a needle phobia (immunotherapy group) and the other because of family reasons (placebo group).

developed. The remaining 35 subjects formed the analysis dataset. Two of these 35 subjects stopped immunotherapy just before the second pollen season, one because of a needle phobia (immunotherapy group) and the other because of family reasons (placebo group), but both continued to provide study data during the second pollen season. The 2 treatment groups were similar at baseline (Table I). A total of 122 other subjects were screened as potential subjects for the study but did not meet the inclusion criteria. They were similar in age to those enrolled but in general had milder grass pollen-related disease and more problems with other allergens (data not shown).

Asthma symptom-medication score

Diary data were available for 1783 (86%) of a possible 2065 days during the second pollen season. There was a substantial reduction in the asthma symptom-medication score ($P = .04$) in the actively treated group compared with the placebo group. The median daily asthma symptom-medication scores were 1.0 (interquartile range [IQR], 0.4-2.0) in the placebo group and 0.5 (IQR, 0.1-0.9) in the active group (Table III). A clear difference was seen between the asthma symptom-medication score in the active and placebo groups throughout the pollen season, particularly during the peak pollen season (Fig 2). There was a trend toward a reduction in the total corticosteroid score in the second pollen season in the active immunotherapy group (median score of 0.7 vs 1.6 in the placebo group,

TABLE III. Asthma symptom-medication scores

	First season			Second season		
	Active group	Placebo group	P value*	Active group	Placebo group	P value*
No. of subjects	18	17	—	18	17	—
Median symptom scores (IQR)	0.9 (0.4-1.8)	1.5 (0.5-2.3)	.52	0.5 (0.1-0.8)	0.8 (0.4-2.1)	.07
Median medication scores (IQR)	0.6 (0.0-1.5)	1.4 (0.5-1.9)	.21	0.5 (0.0-1.7)	1.2 (0.0-3.2)	.56
Weighted† median symptom-medication scores (IQR)	1.0 (0.7-1.8)	1.5 (0.4-2.2)	.35	0.5 (0.1-0.9)	1.0 (0.4-2.0)	.04

Comparison of weighted symptom-medication scores for each group for both pollen seasons using the analysis data set.

*Wilcoxon 2-sample sum rank test for comparison between median scores for active and placebo groups.

†Weighted by inverse variance of symptom and medication scores.

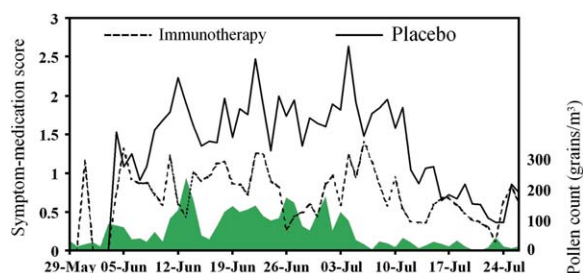


FIG 2. Grass pollen counts and symptom-medication scores for the second summer. Daily atmospheric grass pollen counts are shown (green area, grains per cubic meter). Asthma symptom-medication scores for the second summer for the active (dotted line) and placebo (continuous line) groups are also plotted on the graph.

$P = .16$) and no difference in the use of inhaled bronchodilators between the 2 groups (median score of 0.4 vs 0.6 in the placebo group, $P = .38$).

Cutaneous, conjunctival, and bronchial allergen reactivity

Allergen reactivity was similar in the 2 groups at baseline (Fig 3). After the first and second pollen seasons, there were statistically significant differences between the 2 treatment groups for cutaneous ($P = .003$ and $P < .001$, respectively) and conjunctival ($P = .002$ and $P = .03$, respectively) allergen reactivity (Fig 3). There was also a statistically significant increase in the allergen required to produce a reaction in the skin, eyes, and lungs in the active group compared with the placebo group after the first and second pollen seasons (Fig 3).

Lung function

The baseline median percent predicted FEV₁ (SE) was normal in the active (101%; IQR, 85% to 105%) and placebo (106%; IQR, 98% to 121%) groups. Thirteen active and 16 control subjects provided lung function data during the second pollen season. Subjects in both groups had an FEV₁ of less than 85% of predicted value a third of the time.

Airway inflammation

Exhaled nitric oxide was measured in 23 subjects (9 in the active group and 14 in the placebo group) during the

second season. There was no difference in the highest standardized exhaled nitric oxide (FE_{NO}) value recording in the active and placebo groups (median of 1.77 [IQR, 1.56-2.13] and 1.99 [IQR, 1.44-2.50], respectively). Induced sputum was collected from 16 subjects (6 in the active group and 10 in the placebo group) during the second pollen season. The number of eosinophils per gram of sputum was similar in the active and placebo groups (45.5×10^4 [IQR, 20.8-144.5] and 44.0×10^4 [IQR, 10.5-78.1], respectively).

Adverse events

Fifty-four treatment-related adverse events were reported, 34 in the active SIT group, reported by 13 (72%) subjects, and 20 in the placebo group, reported by 7 (41%) subjects. There were 24 local adverse events, 13 and 11 in the active and placebo groups, respectively. These episodes of pruritis, pain, or swelling were expected consequent to subcutaneous allergen or histamine injection. They were well tolerated with symptomatic treatment with antihistamines and ice. Thirty adverse events were classified as systemic, with 21 and 9 in the active and placebo groups, respectively. Most were episodes of eczema, urticaria, or rhinoconjunctivitis. There were 7 pulmonary adverse reactions in 7 subjects, 4 in the active group and 3 in the placebo group. Four reactions occurred during up dosing, and 3 occurred during the maintenance phase. All were clinically mild and responded immediately to inhaled bronchodilator. None required intramuscular adrenaline. Where there was a reduction in peak flow, this was always less than 20%. Two pulmonary reactions occurred more than an hour after an injection. One child had a cough 2 hours after active treatment, and another had chest tightness 2 hours after a placebo injection. There were no withdrawals from the study because of adverse events.

DISCUSSION

We have assessed the efficacy of SIT in a group of asthmatic children and teenagers whose symptoms are primarily caused by grass pollen. Only 39% of the families correctly guessed to which group they were assigned before unblinding (53% and 25% of the immunotherapy

and placebo groups, respectively), whereas 39% (33% and 44%, respectively) stated that they were not sure. This suggests that blinding was achieved. The study demonstrates that SIT is an effective therapy for seasonal allergic asthma in this group. It was effective throughout the pollen season, particularly when the pollen count was high (Fig 2). The significant improvement in asthma symptom-medication score was accompanied by significant reductions in allergen sensitivity in the skin, eyes, and lungs when compared with that seen in the placebo group.

Our results are comparable with those of other studies looking at the efficacy of grass pollen immunotherapy in adults. Typical results are a 50% to 77% reduction in asthma symptoms^{1,15-17} and a 50% to 66% reduction in medication use,^{15,17,18} as summarized by the systematic review by Abramson et al.⁴ A significant reduction in the symptom-medication score was not seen in the first year of the study because there was a smaller difference between the immunotherapy and placebo groups. Other groups have found that immunotherapy is more effective in the second year compared with the first year of treatment.¹⁷ This might be because many subjects only finished up dosing a few weeks before the first pollen season. In support of this, there was a trend toward the symptom-medication score in the immunotherapy group being lower in the second pollen season than in the first ($P = .06$). No such difference was seen in the placebo group ($P = .40$). Also, in our study there was a lower pollen exposure in the first season compared with that in the second season, which might have compromised our ability to detect significant differences between the 2 groups in the first season.

Immunotherapy was shown to lead to substantial reductions in reactivity to grass pollen in the skin, conjunctiva, and lungs (Fig 3), as in previous studies.^{1,19,20} Like previous studies, we failed to demonstrate a significant effect on lung function,⁴ although a seasonal decrease in lung function was seen in both groups during the pollen season. Such a result is perhaps not surprising because (1) the treatment protocol was designed to minimize symptoms and therefore abnormal lung function and (2) not all the subjects were able to provide lung function data. To our knowledge, airway inflammation has not been previously used as an outcome measure in a pediatric asthma immunotherapy study. Allergic airway inflammation in the immunotherapy and placebo groups was assessed by using both induced sputum morphology and exhaled nitric oxide.²¹ Previous studies demonstrate that sputum eosinophilia and FE_{NO} increase when inhaled steroid dosages are reduced.²² This study suggests that immunotherapy might have a steroid-sparing anti-inflammatory effect in the airway because airway inflammation was similar in both groups, despite the immunotherapy group receiving only half the corticosteroid dose compared with that of the placebo group. A previous study has shown that immunotherapy with house dust mite decreased the late-phase response in asthmatic children.²³ Also, despite the trend toward a reduced use of corticosteroids in the immunotherapy group, reliever bronchodilator use was not increased in this group, suggesting that subjects were not

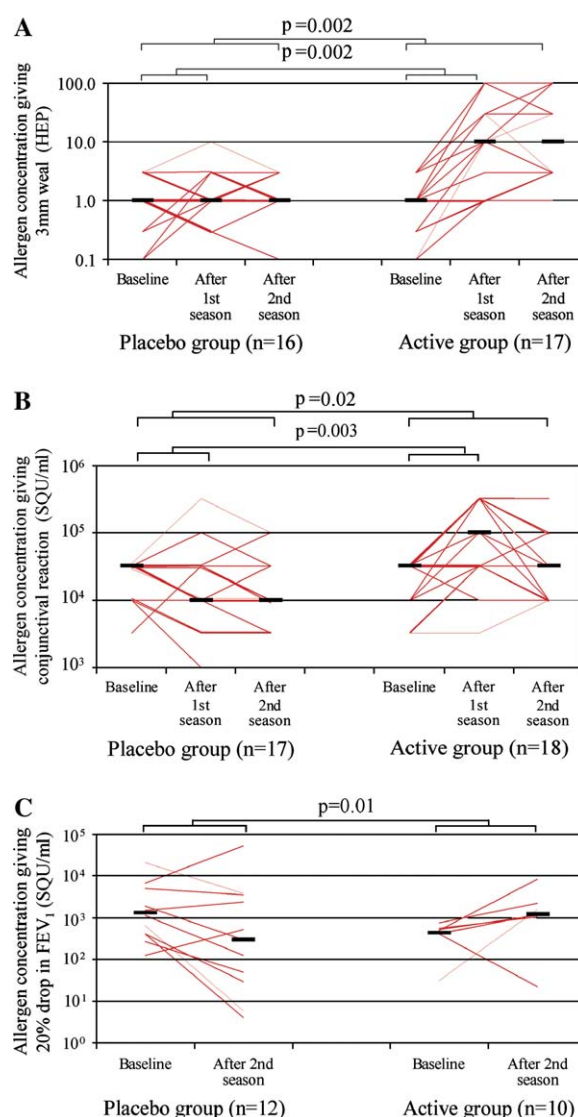


FIG 3. Change in cutaneous (A), conjunctival (B), and bronchial (C) allergen reactivity. Results represent the allergen concentration producing a 3-mm wheal (A), conjunctival reaction (B), or 20% FEV₁ decrease (C). Lines represent subjects, and some subjects overlap. Black lines represent median values. Groups are compared with the Wilcoxon 2-sample rank sum test.

simply switching from using inhaled corticosteroids to bronchodilators. The 2 groups had been expected to use equivalent quantities of bronchodilator because corticosteroid doses were adjusted to minimize symptoms and bronchodilator use.

In this study both a topical anesthetic cream and an antihistamine were given before immunotherapy injections. Prophylactic antihistamines might reduce the risk of adverse effects associated with immunotherapy.⁹ Topical anesthetic cream seems not to have been used previously for immunotherapy. There is one report of it being used for intradermal skin testing, where it was shown not to alter the wheal size.²⁴ All the subjects reported minimal pain with injections. Only one subject had a needle phobia,

which led her to stop immunotherapy injections before the end of the study. A number of subjects experienced pulmonary adverse reactions, but these were seen in both the immunotherapy and placebo groups, with symptoms being mostly mild and well tolerated. This suggests that these minor respiratory reactions might have been due to environmental factors and not the immunotherapy. The absence of significant systemic reactions in this group of children with moderate asthma emphasizes the safety of this approach. Additionally, no subject was withdrawn from immunotherapy as a result of adverse effects or perceived lack of efficacy.

This study has demonstrated that grass pollen immunotherapy is an effective treatment for asthma in children and teenagers who are monoallergic to grass pollen. Our work extends the findings of the PAT study,²⁵ which demonstrated that immunotherapy reduces both the symptoms of rhinoconjunctivitis and the progression from hay fever to asthma in childhood. We have shown that even once significant asthma is established in childhood, immunotherapy has an important therapeutic role. Grass pollen allergy persists over many decades, causing systemic allergic symptoms and impairing quality of life in children and teenagers. Because the clinical benefits of SIT have been shown to modify the long-term natural history of disease in adults,² this treatment modality should be of particular interest in the pediatric population.

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