

SPECIFIC IMMUNOTHERAPY HAS LONG-TERM PREVENTIVE EFFECT OF SEASONAL AND PERENNIAL ASTHMA: 10-YEAR FOLLOW-UP ON THE PAT STUDY

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The Preventive Allergy Treatment (PAT) study; a prospective long-term follow up study, that evaluated one hundred and forty-seven grass and or birch pollen allergic patients (ages 16-25) 7 years after initiation of a 3 year treatment of subcutaneous specific immunotherapy (SIT). One hundred seventeen ($n=117$) were analyzed for long-term clinical effect and asthma development at the end of the 10 year period. Twenty four of fifty three developed asthma among the control group and sixteen of sixty four of the actively treated SIT patients. Longitudinal treatment effect was adjusted for bronchial hyper-responsiveness and asthma status at baseline to including observations noted at 3, 5, 10 year follow up ($n=511$) and included all children with and without asthma at baseline ($n=189$) was significantly significant ($P=0.0075$). The odds ratio for no-asthma being 4.6, 95% CI (1.5-13.7) in favor of SIT.

Conclusion: Specific immunotherapy in children with allergic rhino conjunctivitis demonstrated long term clinical effects as well as preventative effect for development of asthma.

Original article

Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study

Background: 3-year subcutaneous specific immunotherapy (SIT) in children with seasonal allergic rhinoconjunctivitis reduced the risk of developing asthma during treatment and 2 years after discontinuation of SIT (5-year follow-up) indicating long-term preventive effect of SIT.

Objective: We evaluated the long-term clinical effect and the preventive effect of developing asthma 7-years after termination of SIT.

Methods: One hundred and forty-seven subjects, aged 16–25 years with grass and/or birch pollen allergy was investigated 10 years after initiation of a 3-year course of SIT with standardized allergen extracts of grass and/or birch or no SIT respectively. Conjunctival provocations were performed outside the season and methacholine bronchial provocations were performed during the season and winter. Asthma was assessed by clinical evaluation.

Results: The significant improvements in rhinoconjunctivitis and conjunctival sensitivity persisted at the 10-year follow-up. Significantly less actively treated subjects had developed asthma at 10-year follow-up as evaluated by clinical symptoms [odds ratio 2.5 (1.1–5.9)]. Patients who developed asthma among controls were 24/53 and in the SIT group 16/64. The longitudinal treatment effect when adjusted for bronchial hyper-responsiveness and asthma status at baseline including all observations at 3, 5 and 10 years follow-up (children with or without asthma at baseline, $n = 189$; 511 observations) was statistically significant ($P = 0.0075$). The odds ratio for no-asthma was 4.6 95% CI (1.5–13.7) in favor of SIT.

Conclusion: A 3-year course of SIT with standardized allergen extracts has shown long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment.

Clinical implication: Specific immunotherapy has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment termination.

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Allergic rhinoconjunctivitis is a major risk factor for later development of asthma (1, 2). More than 20% of all children with rhinoconjunctivitis develop asthma later in life and rhinitis frequently precedes the onset of asthma. Although not specifically designed for this purpose, other studies have indicated the preventive potential of specific immunotherapy (SIT) in reducing the risk of asthma in patients with allergic rhinoconjunctivitis (3–6). A recent study on a 3-year course of co-seasonal sublingual immunotherapy has also shown the potential of prevention of seasonal allergic asthma in grass pollen allergic children suffering only from rhinitis (7).

The Preventive Allergy Treatment study (PAT) is the first prospective long-term follow-up study that tested whether SIT can prevent the development of asthma and whether the clinical effects persist in children suffering from seasonal allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen as these children grow up. The total SIT period was 3 years, after which the children were evaluated for the development of asthma. The patients were re-evaluated after a total of 5 years. The evaluation showed that immunotherapy impedes progression from allergic rhinoconjunctivitis to asthma after 3 years of SIT (8) and at the 5 year follow-up 2 years after treatment termination (9). The actively

treated children had significantly less asthma after 3 years of SIT (odds ratio 2.5; $P < 0.001$) and at the 5 year follow-up (odds ratio 3.1; $P < 0.01$) as evaluated by clinical symptoms in favor of SIT for prevention of development of asthma and significantly less patients reported an increase in asthma scores. Furthermore, the significant improvement in allergic rhinoconjunctivitis and conjunctival provocation test (CPT) results observed after 3 years of SIT persisted at the 5 year follow-up.

The present study investigated whether these clinical effects along with the preventive effect of developing asthma persisted 7 years after termination of SIT (at 10 year follow-up).

Methods

Patients

A total of 205 children aged 6–14 years from six pediatric centers after a baseline season (0-season) were randomized to 3 years of subcutaneous SIT or to a control group. The children had a clinical history of birch and/or grass pollen induced seasonal allergic rhinoconjunctivitis. Further inclusion criteria were positive skin prick test and CPT results. For a further description of inclusion criteria see Moller et al. (2002)(8). The study design is illustrated in Fig. 1. The patients and/or their parents gave informed consent according to the Helsinki declaration and Ethical Committees approved the study in the respective countries.

Treatments

Patients were included and the treatment was initiated from 1992 to 1994. The patients were stratified on the basis of bronchial responsiveness to methacholine during the 0-season, age, sex and years with allergic rhinoconjunctivitis according to history and then randomized into two groups. To reduce the influence of difference in pollen exposure, randomizations were performed centre for centre. In the controlled design, one group was treated with SIT for 3 years, while the other group served as an open control group. Both groups were followed by the identical measures, except the administration of the allergen injections.

Both groups were allowed to take symptomatic medication limited to loratadine tablets (5–10 mg/day), nasal levocabastine and/or ocular sodium cromoglycate. If necessary, nasal budesonide up to 100 µg/day in each nostril was allowed. In case of asthmatic symptoms, short acting inhaled β₂-agonists were prescribed. When

needed inhaled corticosteroids could be introduced. After discontinuation of SIT, all patients were offered the same drugs as before.

After a 0-season, SIT was initiated with characterized and standardized allergen extracts of grass pollen (*Phleum pratense*) and/or birch pollen (*Betula verrucosa*). Up-dosing was performed with depot extracts (Alutard SQ; ALK-Abelló, Horsholm, Denmark), with weekly injections over 15–20 weeks or as rush immunotherapy with aqueous extracts (Aquagen SQ; ALK-Abelló). Maintenance injections with the depot preparation 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 µg Phl p 5 (grass) and 12 µg Bet v 1 (birch).

Skin prick test

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).

Conjunctival provocation test

Conjunctival provocation tests were performed outside the pollen seasons, always at the same time of the year, before the start of immunotherapy and after 1, 2, 3, 5 (5-year follow-up) and 10 years (10-year follow-up). Half ¹⁰log increments at concentrations from 100 to 1 000 000 SQ units were used (Aquagen SQ; ALK-Abelló) (10).

Methacholine bronchial provocation test

Methacholine bronchial provocation tests (MBPT) were performed during the 0-season(s) before randomization and in the relevant pollen season(s) and during winter. MBPT was performed using the reservoir method (11). The method involves a high quality nebulizer system (Pari Provocation Test 2, Pari, Starnberg, Germany) combined with a 10-l storage bag allowing standardized pulmonary aerosol deposition at saturated ambient temperature and pressure conditions. First 0.9 M NaCl solution and then test solutions 0.5, 1, 2, 4, 8, 16 mg/ml methacholine were nebulized and inhaled. FEV₁ was measured three times before exposure 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 ≥20% decrease in FEV₁ in relation to baseline. The provocative dose (PC₂₀) was estimated by linear interpolation of the two 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.

Visual analogue scale

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

Asthma diagnosis

Asthma was defined as recurrence of at least two of the three following symptoms within the last 12 months: cough, wheeze and

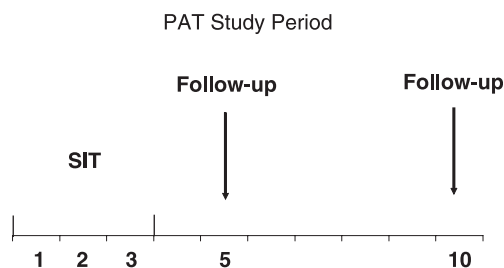


Figure 1. Study design.

shortness of breath. Further demands for the conclusive diagnosis of asthma were that the symptoms were not only triggered by infections and that the patients responded to treatment with β_2 -agonists. Thus, the clinical diagnosis was independent of the level of hyper-responsiveness to methacholine.

Statistical methods

The effect of SIT at 3, 5 and 10 years on prevention of asthma was addressed specifically by analyzing the children without asthma at baseline. Clinically diagnosed asthma was analyzed per centre by Fischer's exact test, and homogeneity of odds-ratios between centers was tested by Zelen's Exact test.

Additionally, a longitudinal data analysis of the probability for 'no asthma' was performed with a mixed logistic regression model. By using a mixed model we obtain information not only from complete observations, but also from incomplete ones, through the conditional expectation of the missing measurements given the observed ones. In the analysis all children randomized and all available data for all follow-up time points have been included. The mixed model included treatment effect (SIT vs control), baseline bronchial hyper-responsiveness and asthma status at baseline as explanatory variables.

Changes from baseline of logarithmic transformed values of CPT were analyzed by ANOVA. Changes from baseline of VAS scores of conjunctivitis and rhinitis and bronchial hyper-responsiveness were analyzed by ANOVA adjusted for baseline values. Two-sided tests and a test significance level of 5% were used.

Results

Initially, 205 children aged 6–14 years were randomized after a baseline season to 3 years subcutaneous SIT or to a control group. One hundred and eighty-three subjects (121 males, 62 females) aged 11–20 years (mean 15.6) participated at the 5-years follow-up. At 10-year follow-up 147 subjects (117 of those had no asthma at inclusion) aged 16–25 (mean 21.0) years were included in the analysis. One centre did not participate in the 10-year follow-up study and 36 subjects were lost for follow-up at 10-year. The flow chart of patient numbers for the study is illustrated in Fig. 2.

Patients without asthma before the start of SIT ($n = 117$) were analyzed for the development of asthma after the 10 year period. The number of patients who developed asthma among controls was 24/53 and in the actively treated group 16/64.

A statistical homogeneity between individual centers was found. According to the definition, asthma development showed an odds ratio of 2.5 (1.1–5.9) in favor of the hypothesis that SIT could prevent the long-term development of asthma (Fig. 3). The odds ratio after 3 years of immunotherapy was 2.5 (1.3–5.1) and 3.1 (1.4–6.9) at 5-year follow-up. Out of those 40 patients reporting asthma at 10 year follow-up, 73% reported asthma during the summer and 55% during the winter.

The final statistical model included treatment, baseline bronchial hyper-responsiveness and asthma status at baseline. The longitudinal treatment effect when adjusted

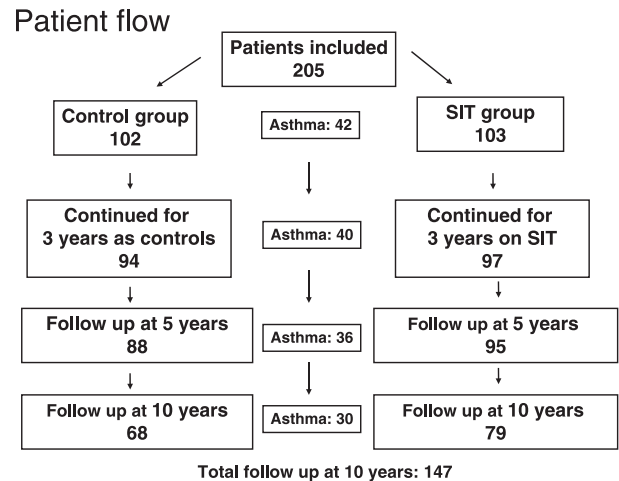


Figure 2. Flow chart of patient numbers. The children with mild to moderate seasonal asthma at baseline are illustrated separately.

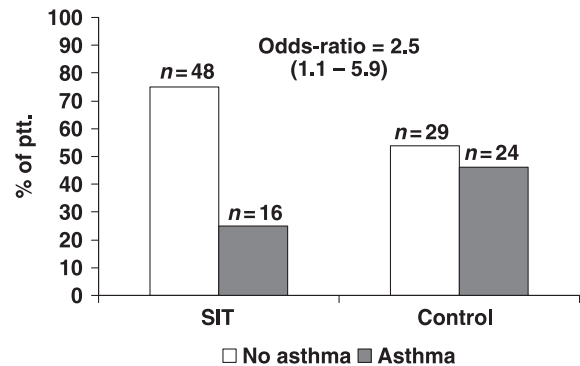


Figure 3. The percentage of children with and without asthma 7 years after termination (10-year follow-up) of specific immunotherapy. Based on the patients without asthma before treatment ($n = 117$). The absolute number of children is shown above the bars.

for bronchial hyper-responsiveness and asthma status at baseline including all observations at 3, 5 and 10 years follow-up ($n = 511$) and including all children with or without asthma at baseline ($n = 189$) was statistically significant ($P = 0.0075$). The odds ratio for no asthma was 4.6 [95% CI (1.5–13.7)] in favor of SIT. Bronchial hyper-responsiveness at baseline was associated with increased risk of later development of asthma ($P = 0.002$). Also an increased probability for having no asthma after 3, 5 and 10 years was demonstrated if the child had no asthma at baseline ($P < 0.0001$).

The clinical effect on conjunctivitis and rhinitis following SIT was persistent 7 years (10-year follow-up) after the termination of treatment. According to the VAS of conjunctivitis and rhinitis, the active group improved significantly more from baseline to 10-year follow-up compared with the control group (–20.9 and –12.4 mm, $P < 0.05$ for conjunctivitis; and –19.9 and –11.5 mm, $P < 0.05$ for rhinitis) (Fig. 4).

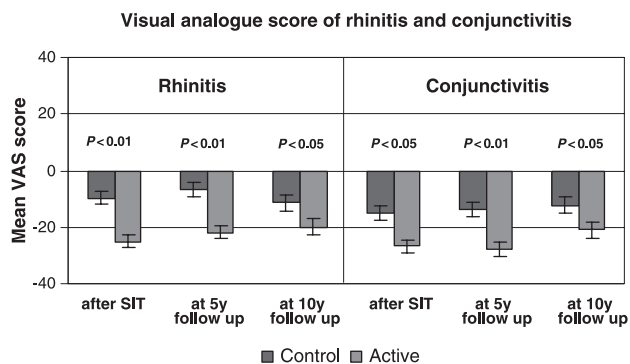


Figure 4. Change from baseline and standard error of the mean for rhinitis and conjunctivitis visual analogue scores at the end of specific immunotherapy, 2 and 7 years after termination.

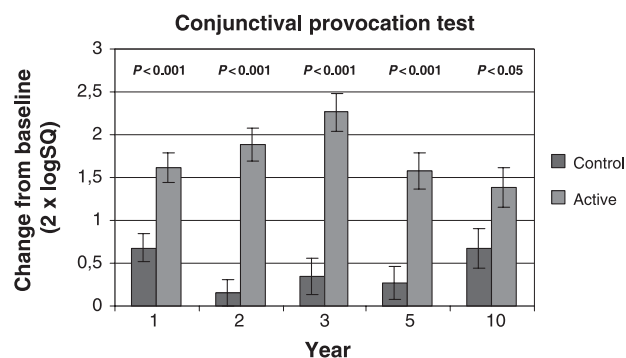


Figure 5. Change from baseline and standard error of the mean for the conjunctival provocation test. For children allergic to both grass and birch, the challenge with both allergens is included.

The conjunctival sensitivity measured by provocation test was significantly reduced in the active group compared with the control group ($P < 0.05$) (Fig. 5).

The groups did not show significant bronchial hyper-responsiveness after 5 and 10 years. The mean (range) seasonal PC₂₀ values for the SIT and control groups at 5 year were 16.7 (0.37–32) and 15.6 (0.03–32) mg/ml. The corresponding winter PC₂₀ values were 22.0 (0.51–32) and 18.9 (0.55–32) mg/ml. At 10-year follow-up the seasonal PC₂₀ values for SIT and control groups were 20.9 (0.34–32) and 21.4 (0.08–32) mg/ml. The winter PC₂₀ values were 22.6 (0.93–32) and 23.9 (0.39–32) mg/ml.

There were no significant differences between the SIT and control group in bronchial responsiveness to methacholine in change from baseline of PC₂₀ after 10 years.

A potential association between the development of new perennial allergies and development of asthma was analyzed. Of those children who developed asthma during the 10-year follow-up, 30% (18 of 61) also developed a positive skin prick test to house dust mites compared with 17% (15 of 86) of the children who did not develop asthma. The difference was not significant. The same

picture was demonstrated for the development of sensitivity to cat or dog allergens. Of those children who developed asthma during 10-year follow-up, 57% (35/61) also developed a positive skin prick test to one or more of the following allergens: house dust mite, cat or dog allergen compared with 50% (43 of 86) of the children who did not develop asthma.

Discussion

This study has demonstrated that the significant clinical outcome achieved during SIT persisted not only at termination of treatment (8) and 2 years after (9) but also 7 years after termination of treatment and that SIT reduced the risk of developing asthma in children suffering from allergic rhinoconjunctivitis at 10-year follow-up indicating a long-lasting benefit of SIT as these children grow up.

In the longitudinal statistical analysis including all subjects at all occasions, we found that bronchial hyper-responsiveness in childhood increased the risk for later development of asthma and that allergen SIT with standardized allergens can prevent the development of asthma.

Various strategies for the prevention of the development of allergic rhinoconjunctivitis and asthma have been proposed including allergen avoidance, pharmacological treatment (antihistamines and steroids) and SIT. Allergen avoidance is hardly applicable to grass and birch pollen allergy and only a limited reduction in exposure can be achieved by the modification of life habits. In contrast, as an inverse relationship between levels of allergen exposure in early life and allergy symptoms has been indicated in some studies, suggesting that exposure to high levels of allergen may provide protection against sensitization (12–14), a new approach in primary prevention has recently been initiated by the Immune Tolerance Network (collaborative research under the National Institute of Allergy and Infectious Diseases) (15). This study is the first in which high-risk children who are sensitized to food but not sensitized to inhalants is given an inhalant allergen mixture (grass, house dust mites and cat) sublingually to prevent them from developing further allergic sensitization and asthma.

Secondary prevention addressing diseased children to prevent symptom and further disease progression involves traditional pharmacotherapy with antihistamines. While this treatment provides symptomatic relief and disease control, this does not modify long-term outcomes in children as the natural course of the disease is not altered. A recent large multi-centre trial in which children with atopic dermatitis were given cetirizine failed to reduce the development of asthma (16).

As a potential tertiary preventive measure for worsening of asthma by early treatment with inhaled steroids in

children with episodic wheezing has been suggested, but recent studies on the capacity of inhaled steroid therapy during early symptomatic episodes of wheezing to delay progression to persistent disease has failed to show any preventive potential (17, 18).

While the persisting long-term clinical effect after termination of SIT has been demonstrated previously (5, 19–23), the PAT study is the first prospective long-term follow-up study to demonstrate that SIT can prevent the development of asthma 7 years after the termination of treatment in children suffering from seasonal allergic rhinoconjunctivitis, and that it is possible to interfere with the natural course of allergic disease.

In contrast to the results at the termination of SIT in the present study (8) and other studies e.g. (4) but in concordance to 5-year follow-up (9), bronchial responsiveness to methacholine showed no statistical significant differences between active and control groups at the 10-year follow-up. As at 5-year follow-up, this may be explained by a spontaneous improvement of bronchial responsiveness over time as a natural improvement in bronchial responsiveness from infancy to adulthood has been reported (24, 25). In the literature it is suggested that patients with rhinitis who also have bronchial hyper-responsiveness are more likely to develop asthma (26). Our study demonstrated that children with rhinitis and

bronchial hyper-responsiveness at baseline were those most likely to develop asthma demonstrating that bronchial hyper-responsiveness may predict the risk for later asthma development.

We also investigated if development of new perennial allergen sensitivities were associated with the development of asthma. Although our data indicated that more children with asthma had developed sensitivity to house dust mites, our study can not confirm this hypothesis. Testing of this hypothesis will require more investigations.

In conclusion, this 10-year follow-up study demonstrates that SIT for 3 years with high-dose standardized allergen extracts shows persistent long-term effect on clinical symptoms after termination of treatment and long term, preventive effect on later development of asthma in children with seasonal rhinoconjunctivitis. In this light, SIT should be recognized not only as first line therapeutic treatment for allergic rhinoconjunctivitis but also as secondary preventive treatment for respiratory allergic diseases.

Acknowledgment

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POLLEN IMMUNOTHERAPY REDUCES THE DEVELOPMENT OF
ASTHMA IN CHILDREN WITH SEASONAL RHINOCONJUNCTIVITIS (THE
PAT-Study)

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A study to determine if a 3 year treatment with specific immunotherapy (SIT) in children with allergic rhino conjunctivitis will prevent the development of asthma and decrease bronchial hyper responsiveness. Two hundred and five children from six pediatric allergy centers (ages 6-14) with positive grass and/or birch pollen allergy were randomized to either open control group or to receive specific immunotherapy. Participants had moderate to severe hay fever symptoms. None were in need of daily asthma treatment. A limited use of medications included loratadine, levocabastine, sodium cromoglycate, and nasal budesonide. Asthma was evaluated by peak flow. During season(s) and winter, methacholine challenge was utilized. Of the 40 (20%) children with mild asthma at randomization, two were free of asthma after 3 years. Children without asthma before start of SIT (n=151) were analyzed for asthma development at the 3 year mark (odds ratio, 2.52; $P < .05$). Significant improvement for methacholine challenge was seen in the active group ($P < .05$). This study concluded that a 3 year treatment course of SIT in children with rhino conjunctivitis not only improved bronchial hyper responsiveness but also reduced the risk of asthma development.

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

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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*). Updosing 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 ¹⁰log 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.

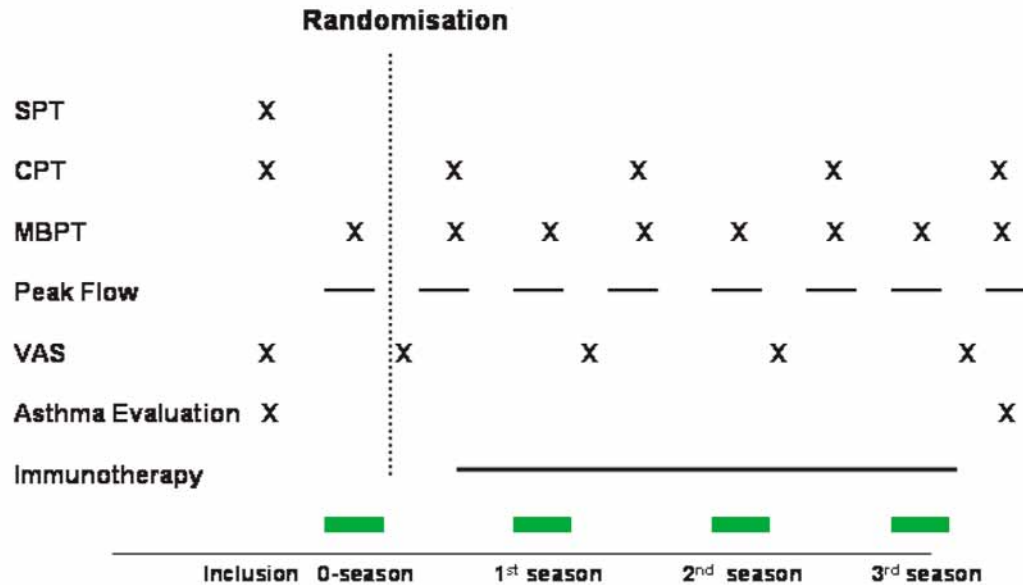


FIG 1. Flow chart of the study.

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 ($P < .001$).

Asthma, rhinitis,
other respiratory
diseases

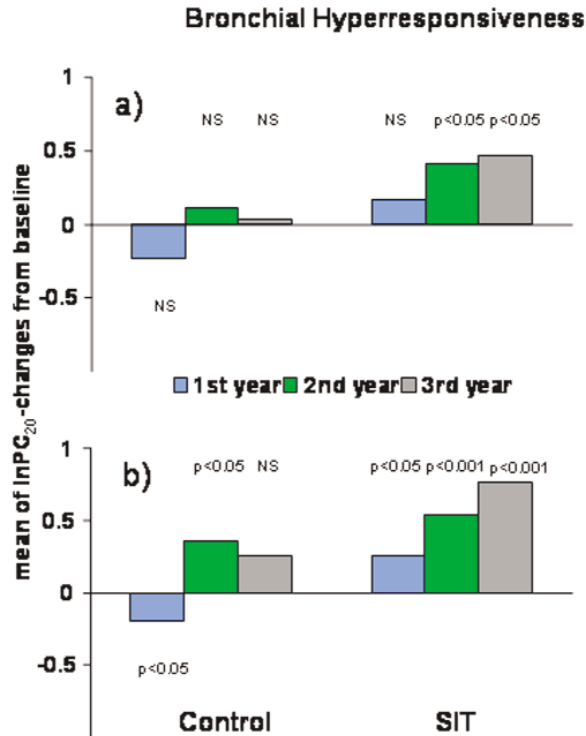


FIG 2. Development of BHR (methacholine challenge test) within each group measured as natural logarithm of PC_{20} change from baseline (a) in the season of pollen exposure and (b) during the winter.

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

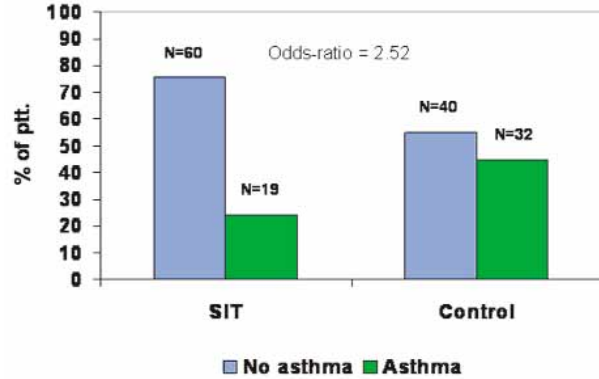


FIG 3. The percentage of children after 3 years of immunotherapy with and without asthma among those without asthma before treatment (N = 151). The absolute numbers of children are shown above the bars.

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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ASTHMA AND PEAK FLOW IN CHILDREN

Asthma is defined as episodic and reversible airflow obstruction and is the most common chronic illness of childhood (2). Children can often appear well and without symptoms between episodes of wheezing or cough (5). Common triggers for pediatric asthma symptoms include allergen exposure, viral illnesses, cold air, irritant exposure, exercise, environmental air pollution, and tobacco smoke (5). Although allergen immunotherapy is a safe and effective treatment for allergic rhinitis and allergic asthma, current guidelines stress caution in administering immunotherapy to those whose asthma is poorly controlled (3, 4). An easy and affordable means to assess lung function is by peak flow meter.

Measurement of peak expiratory flow rate (PEFR) by peak flow meter represents the maximum expiratory flow rate after your child has inhaled to his/her total lung capacity. Because each child is unique (age, sex, height) his/her peak flow-based asthma treatment plan is based on their own peak flow reading (1). An assessment of your child's health should be made prior to administering immunotherapy in order to determine if there has been a recent change in his/her health which may require withholding immunotherapy and/or modifying his/her current treatment (3). In essence, the intention of assessing peak expiratory flow is to alert the parent and provider that a more in depth assessment and/or intervention may be warranted. Instructions for using a peak flow meter as well as ascertaining your child's personal best as taken from www.healthychildren.org (1) follow below:

How to use a peak flow meter:

1. First set the pointer at zero.
2. Stand in a comfortable, upright position.
3. Hold the peak flow meter (horizontally) and keep fingers away from the pointer.
4. Take a deep breath and close lips firmly around the mouthpiece. Keep tongue clear of opening.
5. Blow as hard and as fast as you can. (For children, an example would be for them to "blow out the candles on the birthday cake".)
6. Check the pointer and record the reading.
7. Reset the pointer back to zero.
8. This procedure is repeated three times and the highest reading is recorded.

How to obtain your child's personal best peak flow number:

The personal best peak flow is the highest peak flow value a child can achieve over a 2-3 week period when his/her asthma is under good control.

1. Take and record the child's peak flow each day for 2-3 weeks.

2. Peak flow should be obtained as close to noon and 2:00 pm each day as possible. The highest peak flow number during the 2-3 week period is considered the child's personal best. Personal best can change over time as disease is controlled and as child grows.

Your provider may periodically readjust your child's personal best.

Note: This procedure is for finding out your child's personal best. To check your child's asthma each day, the reading will be obtained and recorded in the morning. For administering for immunotherapy purposes, peak flow readings will be obtained and recorded 30 minutes prior to injection (4).

How to use personal best number to set a child's peak flow zones:

Knowing your child's personal best peak flow number can be very helpful in monitoring day to day lung function and variability and serve as a guide for treatment/management of his/her asthma (5). Keep a daily record of peak flow readings. If the medication prescribed is working, you should see an improvement in peak flow readings. The following color zone below is commonly used when monitoring peak flow (1).

THE TRAFFIC LIGHT SYSTEM:

Green Zone:

Peak expiratory flow rate ("PEFR") 80-100% of personal best. All systems "Go", child is relatively symptom-free and can maintain current asthma management program. If on continuous medication and peak flow is constantly in the green zone with minimal variation, your provider may choose to gradually decrease medication.

Personal best PEFR 80/100 is lower limit of Green zone.

Yellow Zone:

PEFR 50-80% of personal best. "Caution", asthma is worsening. A temporary increase in asthma medication is indicated. If child is on chronic medications, maintenance therapy will probably need to be increased. Contact your child's provider to fine-tune therapy.

Personal best PEFR 50/100 is the lower limit of yellow zone.

Red Zone:

PEFR below 50% of personal best. "Danger", asthma management and treatment is failing to control symptoms. Inhaled bronchodilator is indicated. If peak flow readings do not return to at least the yellow zone, contact your child's provider who will help employ more aggressive therapy. Maintenance therapy will have to be increased.

Personal best PEFR 50/100 is the highest limit of red zone.

The traffic light zones per www.healthychildren.org (1) are broad guidelines designed to simplify asthma management. Successful control of asthma depends upon a partnership between patient/parent and provider. This open communication and exchange of information can be improved with peak flow monitoring and reporting. Your provider can use this data to design and adjust your child's asthma medication to achieve the best asthma control possible for him/her.

Normal Predicted Average Peak Expiratory Flow for Children
(in liters/minute)

<u>Height</u> <u>(inches)</u>	<u>Peak</u> <u>Flow</u>	<u>Height</u> <u>(inches)</u>	<u>Peak</u> <u>Flow</u>	<u>Height</u> <u>(inches)</u>	<u>Peak</u> <u>Flow</u>
43	147	51	254	59	360
44	160	52	267	60	373
45	173	53	280	61	387
46	187	54	293	62	400
47	200	55	307	63	413
48	214	56	320	64	427
49	227	57	334	65	440
50	240	58	347	66	454

Normal Predicted Average Peak Expiratory Flow (Post-pubertal)

Males					Females				
<u>60"</u>	<u>65"</u>	<u>70"</u>	<u>75"</u>	<u>80"</u>	<u>55"</u>	<u>60"</u>	<u>65"</u>	<u>70"</u>	<u>75"</u>
55	60	26	49	69	37	40	26	49	65

References

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