

Short communication

Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen

In a retrospective study, asthmatic patients allergic to either house-dust mite (HDM) (*Dermatophagoides pteronyssinus*) ($n=34$) or to both HDM and grass pollen (GP) ($n=14$), and who were treated with specific immunotherapy (SIT) during childhood (mean duration of SIT: 61 ± 9.70 months), were re-evaluated in early adulthood after mean cessation of SIT for 9.3 ± 2.76 years. The results were compared to those of a control group of asthmatic patients ($n=42$) with comparable asthma features, who were treated with appropriate antiasthmatic drugs during childhood, but who never received SIT. Re-evaluation was carried out with a standardized questionnaire, skin prick tests (SPT), and lung-function assessments. At the time of re-evaluation, the mean age in the SIT-treated group was 23.1 ± 3.50 years; in the control group, it was 22.7 ± 3.40 years. At re-evaluation, the risk of frequent asthmatic symptoms was three times higher in the control group than in the SIT-treated group (prevalence ratio: 3.43; $P=0.0006$). The frequent use of antiasthmatic medication was also more pronounced in the control group, although the difference was not statistically significant ($P=0.38$). Lung-function parameters and results of SPT with HDM were comparable in both groups. It is concluded that SIT has long-term effects on asthmatic symptoms in young adults.

M. Cools, H. P. Van Bever

Department of Pediatrics, University of Antwerp,
Antwerp, Belgium

J. J. Weyler

Department of Epidemiology, University of Antwerp,
Antwerp, Belgium

W. J. Stevens

Department of Immunology, University of Antwerp,
Antwerp, Belgium

H. P. Van Bever
Department of Pediatrics
University Hospital Antwerp
Wilrijkstraat 10
2650 Edegem – Antwerp
Belgium

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In several double-blind, placebo-controlled studies, the clinical effect of specific immunotherapy (SIT) has been clearly demonstrated in both children and adults (1–4). On the other hand, maintenance treatment, including use of inhaled corticosteroids and disodium cromoglycate, allows sufficient control of asthma in most patients (5–9). The interest in SIT has been rising over the last 10 years since it was suggested that this kind of treatment may have some additional effects to the pharmaceutical treatment: SIT is believed to induce specific changes in the immune system (10–16), thereby influencing the long-term prognosis and outcome of asthma (17–22).

The aim of the present study was to examine the long-term outcome of a group of asthmatics treated with medication and SIT during childhood, compared to the long-term outcome of a group with comparable asthma features who received only appropriate antiasthmatic medication.

Abbreviations: FEV₁%; forced expiratory volume in 1 s; HDM: house-dust mite; GP: grass pollen; OR: odds ratio; PR: prevalence ratio; SD: standard deviation; SIT: specific immunotherapy; TDA: total dose of administered allergen.

Material and methods

Study design

The first part of this retrospective study consisted of a file study, in which SIT-treated patients and control patients were selected according to strict criteria (see below). Thereafter, all subjects were invited to participate in the study. Re-evaluation was carried out in subjects over 18 years of age who had been symptom-free for at least 4 weeks. They were assessed by standardized questionnaire, clinical examination, skin prick tests (SPT), and lung-function testing. A questionnaire gauged their actual asthmatic symptoms and their use of medication. The symptom and medication scoring evaluated these parameters as absent/seldom (i.e., less than once per week) or frequent (i.e., once per week or more). SPT with *Dermatophagoides pteronyssinus* (house-dust mite [HDM]) was performed with aqueous extracts (Vivodiagnost intradermal test, ALK, Denmark). Control SPT were performed with buffer solution, histamine, and codeine phosphate. Patients using oral corticosteroids or antihistaminics at the time of examination, as well as patients with skin hypo- or

hyperreactivity (i.e., severe atopic dermatitis), were excluded from this part of the study ($n=8$). Lung function was evaluated by assessment of forced expiratory volume in 1 s (FEV₁) with an electronic spirometer (Flowmate, Jaeger, Würzburg, Germany). FEV₁ was expressed as percentage of the predicted value (FEV₁%), according to Zapletal et al. (23). For each participant, the highest value of three consecutive tries was retained.

Selection of SIT-treated patients and control patients

In our hospital, a total of 108 asthmatic children were treated with SIT during the period 1978–92. Sixty-five of them were selected by the following criteria:

- 1) having reached 18 years of age at re-evaluation time
- 2) having suffered from perennial childhood asthma and a documented allergy to HDM ($n=34$) or to both HDM and grass pollen (GP) ($n=14$) (i.e., positive SPT and/or positive specific IgE)
- 3) SIT during at least 3 consecutive years with an HDM extract or a combined HDM plus GP extract
- 4) cessation of SIT for at least 5 years.

Of these 65 SIT-treated patients, the addresses of only 51 could be found. Three of them refused to participate in the study: one patient said she did not have time, and two others said they no longer suffered from asthma and declined to participate in any study about asthma. Thus, 48 SIT-treated patients participated in the present study. The mean time they received SIT was 61 ± 9.70 months. The mean time after withdrawal of SIT at re-evaluation was 9.3 ± 2.76 years.

Forty-two control patients of comparable age (>18 years) were randomly selected from the hospital files according to the following criteria:

- 1) having suffered from perennial childhood asthma and a documented allergy to HDM (i.e., positive SPT and/or positive specific IgE)

- 2) severity of childhood asthma comparable to the SIT-treated group as shown by age of diagnosis of allergic asthma, presence of atopic eczema, FEV₁% at the moment of diagnosis, and use of antiasthmatic medication
- 3) sufficient control of childhood asthma by antiasthmatic medication and never having received SIT.

At the time of re-evaluation, the mean age in the SIT-treated group was 23.1 ± 3.50 years; in the control group, it was 22.7 ± 3.40 years. Allergen-avoidance measures and asthma education were the same in both groups. The clinical data of SIT-treated patients and control patients are presented in Table 1.

SIT during childhood

SIT was administered by a standardized protocol with one type of allergen extract (Allerset, HAL, Haarlem, The Netherlands), as previously described (24). Briefly, the therapy consisted of two phases: a semirush procedure, during which injections were administered twice a week in increasing concentrations, and a maintenance therapy, during which a fixed dose of allergen was injected monthly until the end of treatment, usually 5 years. The maximum dose for HDM was 5000 AU/month (allergy units: 5000 AU = 5–20 μ g of Der p 1 and Der p 2); for GP, it was 10 000 NU/month (Noon units). When the postulated schedule of SIT was strictly observed without any dose reduction (e.g., for reasons of systemic reactions), a total dose of 320 000 AU of HDM was administered during the 5 years of treatment.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD). They were compared by the unpaired Student's *t*-test and one-way analysis of variance (ANOVA). Differences between categoric data were analyzed by the chi-square test (χ^2). To simplify

Table 1. Clinical data of subjects of different groups

	Never SIT	SIT-treated	SIT HDM	SIT HDM plus GP
Number	42	48	34 (71%)	14 (29%)
Male/female	28/14	31/17	24/10	7/7
Antiasthmatic medication* (number)	β -ag: 42 DSCG: 13 IC: 26	β -ag: 48 DSCG: 26 IC: 30		
Mean age at initial diagnosis of allergic asthma (years)	7 ± 4.3	5 ± 3.8	5 ± 3.6	5 ± 4.2
Number (%) of patients with atopic dermatitis	9 (21%)	21 (44%)	13 (38%)	8 (57%)
Mean FEV ₁ % at time of diagnosis	$85\% \pm 17.9$	$84\% \pm 15.7$	$83\% \pm 15.4$	$86\% \pm 16.7$
Mean duration of SIT (months)		61 ± 9.7	62 ± 9.1	59 ± 11.1
Number of years after having stopped SIT		9.3 ± 2.76	8.7 ± 2.91	10.7 ± 1.78

*Antiasthmatic medication used during childhood (β -ag: β -agonists, DSCG: disodium cromoglycate, IC: inhaled corticosteroids).

statistical analysis, asthmatic symptoms and medication use were dichotomized as “none” or “sporadically” in contrast to “frequent”. The associations between SIT and asthmatic complaints and medication use in adult life were quantified by prevalence ratio (PR) and prevalence odds ratio (OR). By logistic regression analysis, these OR were adjusted for the influence of confounding factors (i.e., presence of atopic dermatitis and abnormal lung function during childhood). Results were considered to be statistically significant if $P < 0.05$. All analyses were performed with the Statistica software package (Statsoft, Inc.).

Results

Evolution in the SIT-treated patients compared to the control patients

The evolution of both asthmatic symptoms and use of antiasthmatic medication was favorable in both groups. At the time of the diagnosis of childhood asthma, 90% of the SIT-treated children suffered from frequent asthmatic symptoms, and 94% of them frequently needed antiasthmatic medication. In the control group, this was 79% and 95%, respectively. The mean FEV₁% in the SIT-treated group and the control group at that time was $84 \pm 15.7\%$ and $85 \pm 17.9\%$, respectively. At the time of re-evaluation, all these parameters had improved considerably, but there were some marked differences between both the groups. In the SIT-treated group, 17% mentioned frequent asthmatic symptoms, and 25% still needed antiasthmatic medication frequently, compared to 57% ($P = 0.0006$) and 33% ($P = 0.38$), respectively, in the control group. For this statistically significant difference in asthmatic complaints, the PR was 3.43, while the OR was 6.67 (95% confidence interval: 2.52–17.7). After correction for confounding factors, the OR remained 6.14, suggesting only limited influence by the previously mentioned confounding factors. In the SIT-treated group, the mean FEV₁% had increased to $98 \pm 16.1\%$, whereas in controls the mean FEV₁% had increased to $105 \pm 15.4\%$ ($P = 0.06$). The results of the SPT with HDM at the time of re-evaluation were very similar in both the groups: the mean diameter of the reaction was 4.5 ± 1.72 mm in the SIT-treated group but 5.3 ± 3.12 mm in the control group ($P = 0.17$). The situation of SIT-treated and control patients is summarized in Table 2.

Evolution in SIT-treated group that received HDM extract compared to group that received extract of both HDM and GP

The differences between these two groups in asthmatic symptoms and medication use during adulthood were far less pronounced. Of the population treated with the HDM extract ($n = 34$), 85% suffered from frequent asthmatic symptoms, and 91% of them frequently used medication at the time of diagnosis during childhood.

In the group treated with the combination extract ($n = 14$), frequent asthmatic symptoms and frequent medication use during childhood were recorded in 100% of cases. The mean FEV₁% in this last group was $86 \pm 16.7\%$ at the moment of diagnosis, whereas, in the first group, it was $83 \pm 15.4\%$. At the time of re-evaluation, these parameters had again improved considerably in both groups, but no statistically significant differences were found; frequent asthmatic complaints appeared in 21% of the group treated with the HDM extract and in only 7% of the group treated with the combination extract ($P = 0.26$). Frequent medication use was found in 24% and 29%, respectively ($P = 0.71$). The results of FEV₁% and SPT with HDM were not different between the two groups.

Influence of the total dose of administered allergen on long-term effects of SIT

The total dose of administered allergen (TDA) was calculated in the group that was treated with HDM extract ($n = 34$). For assessment of the effect of the TDA with regard to the long-term effect of SIT, the population that was treated with the pure HDM extract was divided into two groups: those who received 320 000 AU of the HDM extract ($n = 19$) (i.e., the normal TDA after 5 years of treatment according to the standard protocol), and those who received less than 320 000 AU ($n = 15$) (for reasons such as the occurrence of systemic reactions and low therapeutic compliance). In the group that received $< 320\,000$ AU, 5/15 (33%) suffered from frequent asthma-related complaints at the time of re-evaluation, and these five subjects frequently used antiasthmatic medication. In the group that received a total dose of 320 000 AU, the figures were only 1/19 (5%) and 2/19 (10%), respectively. The difference in asthmatic complaints between the two groups was statistically significant ($P = 0.025$); the difference in medication use was of borderline statistical significance ($P = 0.08$).

Discussion

A number of studies have affirmed the immediate and short-term positive effects of SIT in the treatment of childhood allergic asthma (1–3). In recent years, the question has arisen of whether SIT can modify the immune system such that, many years after cessation of SIT, the natural course of childhood asthma is still positively influenced by this treatment. A limited number of studies have examined the long-term effects of SIT on the clinical presentation of asthma. These studies suggest a sustained effect of SIT after 5, 6, and 10 years of follow-up (17–22). This long-term favorable effect of SIT seems to be correlated with the total dose of administered allergen and with the total duration of SIT (18).

Table 2. Situation of SIT-treated patients and control patients

	SIT-treated (n=48)	Controls (n=42)	χ^2	P
Asthmatic complaints			0.07	0.0006
Never	13 (27%)	3 (7%)		
Sporadically	27 (56%)	15 (36%)		
Frequent	8 (17%)	24 (57%)		
Antiasthmatic drugs			0.76	0.38
Never	22 (46%)	12 (29%)		
Sporadically	14 (29%)	16 (38%)		
Frequent	12 (25%)	14 (34%)		
SPT with HDM extract (in mm)	4.5 ± 1.72	5.3 ± 3.12	11.57	0.17
FEV ₁ %	98 ± 16.1%	105 ± 15.4%	1.95	0.06
Δ FEV ₁ %*	12.4 ± 19.4%	20.8 ± 20.07%	1.84	0.07

The first aim of the present study was to examine whether SIT can be considered a disease modifying therapy with regard to the clinical presentation of asthma (asthmatic symptoms, use of antiasthmatic medication, and lung-function tests). These parameters were assessed in both SIT-treated and control patients at the time of diagnosis (in childhood) and 9.3 years later (in early adulthood). The control patients, who were treated with antiasthmatic medication, but who never received SIT, suffered almost 3.5 times more from frequent asthmatic symptoms and used more medication in early adulthood than the SIT-treated group, who had been treated with antiasthmatic medication and SIT during childhood for at least 3 years. This significant difference in asthmatic complaints and use of medication was not reflected in lung-function tests: in early adulthood, normal values for FEV₁% were reached in both groups. Furthermore, SPT with HDM did not reveal significant differences in mean diameter of the reaction. With regard to the evolution of symptom and medication scores and lung function many years after cessation of SIT, the results of this study are in agreement with the literature (17–21). However, as no statistical difference between SIT-treated and control patients could be found in SPT with HDM, the results of other authors could not be confirmed on this point (20, 21).

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In the present study, the outcome of a group of asthmatic patients allergic to HDM and treated with a single HDM extract was compared to the outcome of a group of patients allergic to HDM and GP, and treated with a combined extract of HDM and GP. Previous short-term studies suggest that combined extracts are less effective than pure extracts (2–4, 25). This could only partially be confirmed in the present study with regard to the long-term effects of SIT. In the group treated with the HDM extract, fewer patients suffered from asthmatic symptoms and used medication at the time of re-evaluation than in the group treated with the combined extract. However, these differences, as well as the difference in SPT and FEV₁%, were not statistically significant.

Another aim of this study was to evaluate the importance of the TDA with regard to the long-term effect of SIT. Here also the results are less convincing: the difference in asthmatic complaints between those who received <320 000 AU and those who received 320 000 AU was statistically significant, but the difference in medication use was only of borderline statistical significance. However, it is important to note that those patients for whom it was necessary to reduce the dose, or even to stop SIT too early, might suffer from more severe asthma than the other ones, so that their long-term prognosis was less favorable, independently of the TDA and the duration of SIT.

In general, the present study offers a number of arguments indicating that SIT can modify the long-term prognosis of asthma, especially with regard to the persistence of asthmatic complaints in early adulthood, and also to the continuous use of antiasthmatic drugs. However, the decision to start SIT should still be very carefully considered, since it is a therapy that should be administered for a long period, probably at least 5 years, without dose reduction if possible, in order to reach a total dose of 320 000 AU.

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