

Original article

Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics

Background: The present study evaluated the steroid-sparing effect of subcutaneous SQ-standardized specific immunotherapy (SIT) in moderate and severe house dust mite (HDM) allergic asthmatics.

Methods: Fifty-four adult asthmatics allergic to HDM requiring at least inhaled corticosteroids (ICS) doses equivalent to 500 µg fluticasone propionate daily were randomized to subcutaneous SIT or placebo injections for a period of 3 years. The minimum required ICS dose, 4 week diary of asthma symptom score, use of rescue medication, peak expiratory flow (PEF) measurements and visual analog scale for asthma symptoms were assessed before start of treatment and after 1, 2 and 3 years of treatment.

Results: In patients with moderate and severe asthma, the reduction in ICS was statistical significant after 2 years of treatment ($P = 0.03$) but not after 3 years. The median reductions were 82% and 42% after the third year for active and placebo respectively. In patients with moderate persistent asthma the reduction was statistical significant larger for those treated with SIT compared with placebo after year 2 and year 3. The median reductions after 3 years were 90% for SIT and 42% for placebo ($P = 0.04$). Despite significant steroid reduction, there was no difference in asthma assessments between the two groups. No serious reactions related to SIT injections were seen.

Conclusion: This study shows that SIT with a SQ-standardized HDM extract is safe. An ICS sparing effect was evident in patients with moderate persistent asthma.

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Clinical efficacy of house dust mite (HDM) specific immunotherapy (SIT) in allergic rhinoconjunctivitis and asthma has been confirmed in controlled trials. A beneficial effect for asthma was documented in several studies showing improvement in symptom and medication score by >40% (1, 2). The efficacy has recently been confirmed in a meta-analysis (3). Inhaled corticosteroids are the most widely used anti-inflammatory drug used in increasing doses to control symptoms in mild to severe asthma. Treatment of moderate asthma includes doses of inhaled steroids equivalent to 500 µg fluticasone propionate (FP) and higher doses are recommended for treatment of severe asthma (GINA). Due to the relative flat dose–response curve of inhaled steroid, higher doses provides little further benefits of asthma control, but increases the risk of side effects. Add-on therapy with another class controller is preferred over increasing the dose of inhaled steroids. The purpose of the present study was to evaluate potential reduction in the use of inhaled steroids when immunotherapy is added to the treatment

in patients with moderate and severe asthma due to HDM allergy.

Material and methods

Patients

Patients were recruited from the outpatient clinic of Aarhus Kommunehospital, from general practitioners in the Aarhus area, and by advertising in local radio, newspapers and educational institutions.

Inclusion criteria were: age 18–60 years, allergy to HDM (*Der-matophagoides pteronyssinus*, *D. pter*), shown by positive skin prick test (>3 mm) Soluprick SQ[®] (ALK-Abelló, Hørsholm, Denmark) and allergen-specific IgE in serum, Magic Lite[®] SQ class ≥2 (ALK-Abelló), perennial asthma with regular symptoms requiring long-term treatment with inhaled corticosteroids (ICS; fluticasone propionate equivalent to 500–2000 µg daily), forced expiratory volume in one second (FEV1) >70% of predicted value, a case history of allergy to HDM as the cause of asthma symptoms, fertile women using contraception, and ability to provide signed informed consent.

Patients were excluded if: (i) A positive skin prick test (Soluprick SQ[®]) to cat or dog and daily contact with the pet. (ii) A positive skin prick test (Soluprick SQ[®]) to *Cladosporium herbarium* or *Alternaria alternata*. (iii) Previous HDM immunotherapy. (iv) Use of inhaled long acting β_2 -agonist during the study. (v) Treatment with β -blockers.

Study design

This was a randomized, double-blind, placebo-controlled study including HDM allergic individuals with asthma. Patients were randomized to subcutaneous SIT with Alutard[®] SQ *D. pter* or placebo containing histamine dihydrochloride (ALK-Abelló). A baseline period was followed by 3 year immunotherapy treatment (Fig. 1). During baseline, ICS was stepwise adjusted to define the lowest dose which could maintain asthma control. In case the patient had a need of a daily dose <500 μ g FP, the patient was withdrawn from the study. In the treatment phase, the stepwise reduction of the dose of ICS was repeated (September–December) after 1, 2 and 3 years of SIT. Dose adjustments were not allowed at any other time. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice. It was approved by the local scientific ethics committee (County of Aarhus) and the Danish National Board of Health. All patients signed an informed consent form before entering the study.

Treatment

Principles for reduction of the ICS dose. All patients were treated with inhaled FP (dry powder inhaler). The daily dose of ICS was stepwise reduced every 3 weeks until asthma was no longer controlled. Treatment was then continued with a dose one step higher. The dose steps of fluticasone propionate were 100, 250, 500, 750, 1000, 1500 and 2000 μ g daily.

Unstable asthma was defined when two or more of the following criteria were fulfilled. (i) Increase in total symptom scores over 7 days by ≥ 7 or in daily symptom scores by ≥ 3 over two consecutive days. (ii) Increase in total number of salbutamol inhalations over 7 days by ≥ 7 . (iii) Morning PEF $\leq 90\%$ of baseline for 4 days or more out of seven. (iv) Diurnal variation of PEF $\geq 15\%$ for 4 days or more out of seven.

Immunotherapy. The up-dosing was performed during an 8-week period with two to three injections at each visit followed by maintenance treatment for 3 years. In the maintenance phase, patients received the individual maximum tolerated dose up to a maximum dose of 100 000 SQ-U (corresponding to 9.8 μ g major allergen Der p1/ml.). The interval between injections was 6 ± 2 weeks. The patients in the placebo group received histamine dihydrochloride injections according to the same dose increase and maintenance schedule (0.00001, 0.0001, 0.001 and 0.01 mg/ml). The

regimen was modified in case of reaction to any injection, extended interval between administrations, intercurrent infection or worsening of asthma. In case of systemic reactions the up-dosing schedule was changed to a one injection per week schedule.

Assessments

The patients completed daily diaries during the month of January before start of SIT and after treatment for 1, 2 and 3 years. Asthma symptoms were categorized as breathlessness, cough, wheeze and chest-tightness. The following was recorded in the diaries. (i) Day-time asthma symptoms on a six-point scale (0–5, with 0 indicating no symptoms and five severe symptoms). (ii) Night-time asthma symptoms on a five-point scale. (iii) Patients' subjective evaluation of the disease was assessed by means of a visual analogue scale (VAS; 0–100 with 0 corresponding no symptoms and 100 severe symptoms). (iv) Morning and evening PEF (Mini-Wright peak flow meter; best of three efforts). (v) Use of rescue medication (salbutamol). The exposure to HDM allergen was evaluated every January by mattress dust sampling. No measures were taken for HDM reduction.

All adverse events that occurred during the trial were recorded. Systemic reactions due to SIT were scored according to EAACI Guidelines (4). Local reactions were defined as $> 8 \times 8$ cm in diameter.

Asthma severity

The classification of asthma severity was based according to daily medication regimen and response to treatment. Moderate persistent asthma was defined as treatment with 500–1000 μ g FP daily and severe persistent asthma with > 1000 μ g FP daily. All patients had normal lung function (FEV1 $> 70\%$ of predicted).

Statistical analysis

The primary end-point of the study was reduction in ICS from baseline. The reduction was analysed hierarchically after 3, 2 and 1 years of treatment, thus, avoiding the need for multiplicity correction. Treatment difference between active SIT and placebo was analysed using the Wilcoxon Rank Sum Test on a 5% significance level. Secondary end-points were asthma symptoms score, rescue medication score, VAS, number of adverse events and concentration of HDM in mattresses. Wilcoxon Rank Sum Tests or ANOVAS were applied where appropriate. The primary analysis was based on the Full Analyses Set including patients with moderate or severe asthma. In addition, a sub-group analysis excluding patients with severe asthma (daily use > 1000 μ g FP) was performed. The sample size was calculated using medication score from a previous study in allergic rhinitis where the ratio between the standard deviation and the mean was 0.58 (5). With a power of 80%, 24 patients in

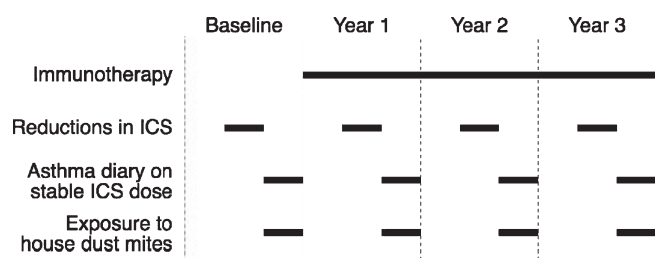


Figure 1. Flow chart of the trial (ICS, inhaled corticosteroids).

each arm were required to detect a difference of 50%. All statistical analyses were performed using the SAS® system (v 8.2, SAS Institute, Cary, NC, USA).

Results

Patients

The two groups were comparable with regard to baseline parameters, i.e. sex, age, dose of ICS, disease duration and PEF (Table 1). A total of 112 patients were willing to participate and were eligible for screening assessment, and 54 of them were randomized into the study. Forty-two of the 54 patients completed the study. Six patients in each group were withdrawn for the following reasons; six for personal reasons, three pregnancies, two development of other diseases, and one in the active group because of asthma attacks induced by the treatment. Figure 2 shows the trial profile according to CONSORT rules (6, 7). As regards sensitization to other allergens 72% of patients were sensitized to *Phleum pratense*, 65% to dog, 52% to cat and 35% to birch pollen.

Reduction in inhaled steroids

Including patients with moderate and severe asthma the median ICS dose reduction was 82% in the active group and 42% in the placebo group after 3 years of treatment ($P = 0.17$). Secondary analysis showed the difference between the two groups was statistically significant for year 2 ($P = 0.03$), with a median reduction of 50% in the active group and 25% in the placebo group. This corresponds to a median dose of 1000 µg FP daily at baseline to a median dose of 250 µg FP daily after 3 years of active SIT treatment. For placebo the median dose went from 750 µg FP daily at baseline to a median dose of 500 µg FP daily. In the *post hoc* analysis of patients with moderate asthma (who required between 500 and 1000 µg FP daily at baseline), a statistical significant reduction in ICS dose was found after 2 years ($P = 0.01$)

Table 1. Baseline characteristics of study population

	Active (n = 26)	Placebo (n = 28)
Sex		
Men	15	17
Women	11	11
Age [years (mean ± SD)]	29.8 (±10.7)	28.5 (±7.1)
Severity of asthma*		
Moderate persistent	20	22
Severe persistent	6	6
Mean duration of asthma [years(±SD)]	14.8 (±9.7)	14.1 (±6.9)
Mean morning PEF ± SD†	511 (±111)	499 (±80.1)

*According to ICS dose at baseline (moderate: >500 and ≤ 1000 µg fluticasone propionate/day, severe: >1000 µg fluticasone propionate/day)

†Measured during 4 week baseline period in January. FEV1 was over 70% of predicted in all patients.

and 3 years ($P = 0.04$). After the second year of treatment, the median reduction in the SIT group was 50% compared with 25% in the placebo group. The median reductions after 3 years were 90% (from a median dose of 1000 µg FP daily to a median dose of 100 µg FP daily) for active IT and 42% (from a median dose of 500 µg FP daily to a median dose of 375 µg FP daily) for patients treated with placebo (Fig. 3).

Asthma symptoms, use of rescue medication, and PEF measurements remained largely unchanged at the annual re-assessments. VAS scores were similar for the two treatment groups (mean values in the active group – baseline: 18, year 1: 21, year 2: 18 and year 3: 16; in the placebo group – baseline: 23, year 1: 24, year 2: 26 and year 3: 24). Four patients in the active group and six

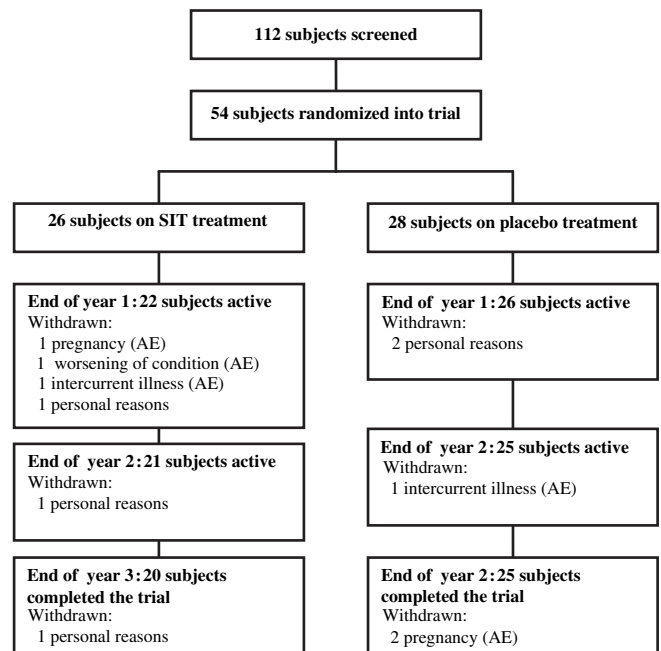


Figure 2. CONSORT disposition diagram.

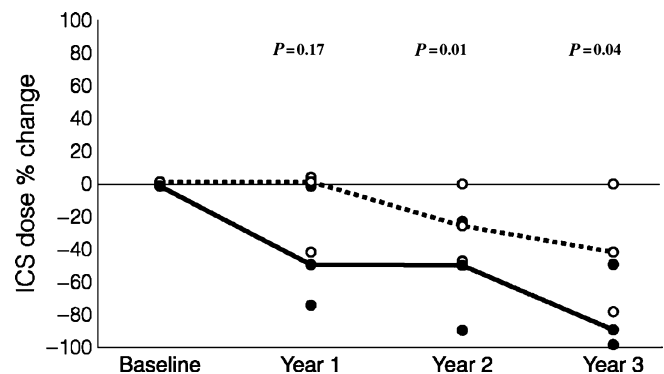


Figure 3. Median % reduction of inhaled steroids in patients with moderate persistent asthma treated with fluticasone propionate > 500 µg and < 1000µg —●— active, -○- placebo with lower 25% and upper 75% quartiles.

patients in the placebo group received short courses of methylprednisolon during the study.

Dosage of specific immunotherapy

In total, 925 injections were administered in the active group and 1013 injections in the placebo group. In the active group (of the 20 patients who completed the study), the recommended 100 000 SQ-U maintenance dose was reached by 11 patients (55%), four patients (20%) reached 80 000 SQ-U and the remaining five patients (25%) had a maintenance dose lower than 80 000 SQ-U. All patients in the placebo group reached maximum dose, but one was adjusted down.

Adverse events related to immunotherapy

There were no life-threatening reaction during the trial and six patients withdrew because of adverse events (three pregnancies, two intercurrent illnesses and one worsening of condition). One patient in the active group experienced severe bronchospasm and was treated with inhalation of nebulised inhaled β 2-agonist and oral corticosteroids. Ten of the 26 patients (38%) in the active group experienced at least one systemic side effect (10 patients had grade 2 reactions and one patient also had grade 3 reactions). In the placebo group, eight of the 28 patients (29%) had a mild (grade 2) or nonspecific (grade 1) systemic reaction (Table 2). Most of the systemic side effects occurred during the up-dosing phase. The total rate of systemic reactions in the active group was 4.7% per injection. The corresponding figure in the placebo group was 2.1%. Subcutaneous nodules were observed in 26% more patients in the active group compared with placebo.

Environmental exposure

Assessment of the concentration of HDM allergen in mattresses showed that all patients were exposed. The majority was exposed to a high level (class 3: >10 mg mites/g dust), and the exposure was unchanged during the study period (Table 3).

Table 2. Adverse reactions after Specific immunotherapy (SIT) or histamine (placebo) injections according to EAAI classification.

Severity grade	Active (n = 26)		Placebo (n = 28)	
	Patients with reactions	No. of reaction	Patients with reactions	No. of reaction
Grade 1 (nonspecific)	0	0	5	9
Grade 2 (mild systemic)	10	41	6	12
Grade 3 (nonlife threatening)	1	2	0	0
Grade 4 (anaphylactic shock)	0	0	0	0
Total number	10	43	8	21

Table 3. Exposure to house dust mites (mattress samples)

Total (μ g/g) [Median (min-max)]	Active	Placebo
Baseline	24 (1-316)	14 (0-587)
Year 1	18 (0-387)	27 (0-495)
Year 2	36 (1-268)	41 (0-419)
Year 3	37 (1-346)	24 (0-780)

Contamination grade is classified as follows: class 0 (low) = 0-2 μ g/g, class 1 (medium) = 2.001-10 μ g/g and class 2 (high) >10 μ g/g.

Discussion

The need for studies investigating SIT efficacy in relation to ICS has been stated (8, 9). In the present study, we assessed the use of ICS in adults with moderate to severe asthma and allergy to HDM when combined with SIT.

ICSs are the most widely used anti-inflammatory medicine providing long-term prevention of the asthma symptoms by suppressing, controlling and reversing inflammation in the airways (10). SIT is an immunomodulatory treatment mostly effective in selected asthma populations (11). Both treatments may alter T-cell dependant responses in asthma patients. SIT have an allergen-specific modifying role in Th2 cell responses either by immune deviation (increase in Th0/Th1) or T-cell anergy (decrease in Th2/Th0) or both (12). ICS reduce the survival of T-cells (13) and thereby influence cytokine production and reverse airway inflammation.

The primary analysis showed that treatment with SIT was numerically superior to placebo at years 1, 2 and 3 in its ability to reduce the use of ICS in HDM allergic asthmatics. The difference was statistically significant at year 2, but did not reach statistical significance at year 1 or 3. A sub-group analysis showed that the greatest effect of SIT was found in the moderate asthmatic subgroup (requiring between 500 and 1000 μ g FP daily), where the treatment difference at 3 years reached statistical significance when compared with placebo. This apparent reduced efficacy in severe asthma patients was also reported by Bousquet et al. (14), who found that severe asthma was a negative predictor of a successful outcome with SIT treatment. Furthermore, SIT has been found to provide clinical improvement when administrated in early stages of allergic disease (15-20).

In general, stepping down trials are difficult to design and it is still unclear which parameters best reflect the changes of bronchial inflammation and long-term asthma control. Some authors suggest that selection of the individual ICS dose by assessment of nonspecific BHR in addition to symptoms and lung function provides a better asthma control (21), and others propose an evaluation of the cellular pattern in induced sputum or in blood to select the optimum ICS dose (22-24). Recent studies demonstrate that NO concentration measurement in exhaled air quantifies airways inflammation and oxidative stress is an optional noninvasive method for

monitoring of therapy (25, 26). However, ICS reduction in the present trial was based on asthma diaries including registration of symptoms, rescue medication scores and assessment of morning and evening PEF. Self-perception of asthmatic symptoms vary between individuals and can be improved by close control at a specialized center with patient-education of the disease process and treatment consequences (27). In clinical trials, when severity of asthma is assessed mainly by diary data, a prominent bias can be observed due to inaccuracies in the recordings of PEF and symptom and medication score. In addition, the presence of a significant placebo effect and overmedication may invalidate correct evaluation of severity. Nevertheless, assessment of symptom score and rescue medication score supplied by PEF measurements is recommended by GINA guidelines and it is a well-recognized approach to control and optimize asthma therapy in daily practice.

In order to minimize the impact of other perennial allergens, all the patients included were predominantly allergic to HDM, i.e. daily contact with domestic animals was disallowed in the case of sensitization to the animals. In our study, 72% of patients were sensitized to grass, 65% to dog, 52% to cat and 35% to birch pollen. In fact, there is an increasing body of evidence showing that a low-dose exposure to dog/cat allergens in public places can contribute to chronic bronchial inflammation and maintain the need for ICS (28, 29). In addition, previous studies (14, 30) showed that bronchial asthma is a multifactorial disease and administration of SIT for a single predominant allergen is less likely to change the course of disease in polysensitized asthmatics. Interestingly, the data of the present trial demonstrated that the reduction of ICS was possible in moderate asthma in spite of a high number of polysensitized patients included in the study.

Several studies suggest that high exposure to HDM can lead to asthma exacerbations and thus prolong the need for preventive treatment with ICS (10). Indeed, the consistently high exposure at home to HDM in both groups in the present trial could possibly mask the steroid-sparing effect of SIT by increasing the need for ICS use.

A clear placebo effect was observed in the control group. The adherence to pharmacotherapy, frequent visits at a specialized clinic and self-education contribute

to better asthma control. All participants were provided with ICS and inhaled salbutamol for free which also may have improved the regular use of ICS. However, the study was double-blind and the same phenomenon apply to the active and placebo groups. The reduction in ICS in both groups is likely a result of prolonged and regular treatment with ICS and not only a pure placebo phenomenon. Regular treatment with ICS over months and years progressively reduce bronchial hyperresponsiveness and reverse aspects of airway remodelling in chronic asthma (31). Regular long-term treatment with ICS therefore leads to a progressive improved asthma control that can be maintained on a lower ICS dose. The results of the present study should be evaluated in light of not only treatment and dose but importantly also in a long-term perspective.

Asthma patients have an increased risk of developing acute systemic side effects after SIT (4). No life-threatening (grade 4) reactions occurred during the study and six patients withdrew due to adverse events, three in each treatment group. The rate of systemic reactions in asthma range from 5% to 35% (32). In the present study, the rate of systemic side effects was 4.7%.

All systemic reactions related to injections except one were mild and occurred mostly during the up-dosing phase. This is in accordance with previously described occurrences (33). In general, the low incidence of side effects in this study may be explained by the carefully individualized dosing, i.e. evaluation of patients' reactions after each injection and meticulous attention to health status before each injection.

In conclusion, the present study shows that SIT with SQ-standardized HDM extract is well-tolerated in HDM allergic asthma patients dependent on moderate to high doses of ICS. When SIT was introduced, the use of ICSs was significantly reduced without loss of asthma control in patients with moderate persistent asthma.

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