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ORIGINAL ARTICLE

Long-term Efficacy of House Dust Mite Immunotherapy in Bronchial Asthma: A 15-year Follow-up Study

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ABSTRACT

Background: Specific immunotherapy for bronchial asthma has been documented to be efficacious in several studies ; however, it is not known whether this efficacy is sustained for several years after cessation of immunotherapy. The aim of this study is to determine the efficacy of house dust mite immunotherapy over a 15-year period.

Methods: This study is an open, parallel, comparative trial in which 31 patients were administered immunotherapy for 5 years and then followed-up for a further 10 years. Their global symptom scores and FEV1 values were compared with another group of 38 patients who refused immunotherapy.

Results: The use of immunotherapy resulted in a statistically significant improvement in both global symptom scores and FEV1 in patients receiving immunotherapy when compared with those in the control group who did not receive immunotherapy. This improvement was sustained for at least 10 years after cessation of immunotherapy.

Conclusions: The benefits of house dust mite immunotherapy are significant and sustained, a decade after its discontinuation.

KEY WORDS

allergy, benefits, bronchial asthma, house dust mite, immunotherapy

INTRODUCTION

Specific immunotherapy (SIT) has been used in the management of allergic diseases since 1911.[1] Several studies have clearly documented the clinical efficacy of SIT in house dust mite allergy, yet this mode of therapy remains controversial,[2] especially in bronchial asthma (BA) despite the fact that 3 meta-analyses have proven the beneficial effects in this condition.[3-5]

A very important question to be answered is whether the effects of SIT are long lasting, particularly after it has been discontinued. If the answer is yes, it would make SIT an attractive, disease modifying, treatment modality for allergic diseases such as asthma and/or rhinitis.

This study is a prospective, open, parallel, comparative trial of SIT versus a control group of patients who did not receive SIT.

METHODS

INVESTIGATIONS

85 selected patients with BA (of more than 512 newly detected BA cases who attended the clinic during the year 1986) were subjected to a detailed history and physical examination. Each patient underwent the following investigations :

(1) Estimation of serum IgE levels (radioimmunoassay)

(2) Skin prick tests (SPT) with a battery of common Indian allergens (ALCIT India Pvt. Ltd., Delhi, India)[6]

(3) Specific IgE levels (RAST) to the house dust mite *D. farinae*.

(4) Spirometry

(5) Peak nasal inspiratory flow rates (PNFIR) using a Youlten's nasal flow meter (Clement Clark International, London, UK).

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CRITERIA

The criteria for selecting patients for this study were :

(1) Symptoms of perennial BA alone, with no evidence of rhinitis or skin allergies. Patients with seasonal BA were excluded from this study so as to avoid intermittent variations in parameters studied. Patients with rhinitis (which in India co-exists with asthma in 55% of cases)[6] were excluded, since variation in symptoms of rhinitis could have falsely altered the patients' perception of asthma symptom scores.

(2) Elevated total serum IgE levels (normal value 0 to 50 IU/ml)

(3) Reduced FEV1 (obstructive airway disease on spirometry).[7]

(4) Normal PNIFR (normal value 100 to 300 L/min)

(5) Positive SPT results (2+ or more) to *D. farinae*.

(6) Positive RAST to *D. farinae* (>class III).

Although an attempt was made to do so, social objections precluded any house dust mite measurements from patients' homes. Patients who had been previously treated with SIT or those in whom there were any known contraindications for administering SIT were excluded from this study. Every patient was found to have taken some form of therapy for BA prior to this study, including oral and inhaled corticosteroids and beta2-agonists ; hence, a washout period of 3 months preceded the beginning of the trial during which only inhaled salbutamol was permitted.

A double blind, placebo controlled trial was contemplated, but was not possible in view of the long-term nature of this study.

RANDOMIZATION

A core group of 197 patients were randomly selected using a random allocation table from the 512 new asthmatics that attended the clinic in 1986. Each patient was offered SIT and inhaled corticosteroids (ICS). Beclomethasone dipropionate was the only ICS available in India in the form of MDI when the study was initiated. Patients who accepted SIT but refused ICS were placed in Group 1 (SIT group) and those who refused both SIT and ICS were placed in Group 2 (control group). There were 46 men and 39 women among the 85 patients who were finally selected in both groups :

Group 1 : The specific immunotherapy group (SIT group) had 37 patients (22 men and 15 women), of which 6 patients (4 men and 2 women) dropped out from the study. Thus 31 patients (18 men and 13 women) completed the study with ages ranging from 8 years to 28 years (mean age 19.77 years).

Group 2 : The control group consisted of patients who refused SIT as well as ICS ; it initially consisted of 48 patients (24 men and 24 women) of which 10 patients (4 men and 6 women) dropped out for a final tally of 38 patients (20 men and 18 women) who completed the study. The age range in this group was 11 years to 35 years (mean age 22.61 years).

None of the 85 patients finally selected were prescribed or administered ICS during the entire study period. Since this was a prospective, long-term study, allocation to either the SIT or the placebo group could not be randomized. No attempt was made to stratify the patients during selection or allotment of patients. Informed consent was obtained from every patient (or their parents in case of minors) before induction into the study.

STUDY PLAN

Avoidance Measures

Each patient was given instructions regarding appropriate avoidance measures, depending on their SPT results. Avoidance measures for house dust included removal of carpets, frequent vacuuming, changing bedding to synthetic material such as foam and removal of soft toys. All measures suggested were strictly scrutinized and audited at each clinic visit, so that they would, as far as possible, result in uniform benefits.

Rescue Medication

Patients in both groups were trained in the use of a salbutamol metered dose inhaler (MDI) through a large volume spacer device (750 ml). Each patient was instructed to use salbutamol as a rescue medication only.

SIT Vaccines

Patients in the SIT group were given a course of subcutaneous desensitizing vaccines, which contained the dust mite *D. farinae* alone (Alcit India Pvt. Ltd., Delhi, India). *D. farinae* is a more common allergen in India than D. pteronyssinus.[6] Vaccines were started simultaneously in all 31 patients in the SIT group on January 1, 1987. These were administered in increasing strength, beginning with 1 : 25,000 w/v conc. to a maximum of 1 : 50 w/v conc., in increasing doses (0.1 − 1.0 ml) and decreasing frequency, beginning with twice a week, then once a week and later once in two weeks. The maximal dose of 1.0 ml., 1 : 50 w/v conc., was reached at the end of 30 weeks followed by administration of a once in 2 weeks maintenance dose (1.0 ml, 1 : 50 w/v conc.). Vaccines in the SIT group were administered from January 1, 1987 to December 31, 1991, and then discontinued. Subsequently both groups were asked to continue with avoidance measures and rescue salbutamol until the end of the study on December 31, 2001. During the five-year vaccination period (1987 to 2001), vaccines in India were still quantified as w/v. However, as a part of a later study,[8] it was determined that the strength of the vaccines administered was approxi-

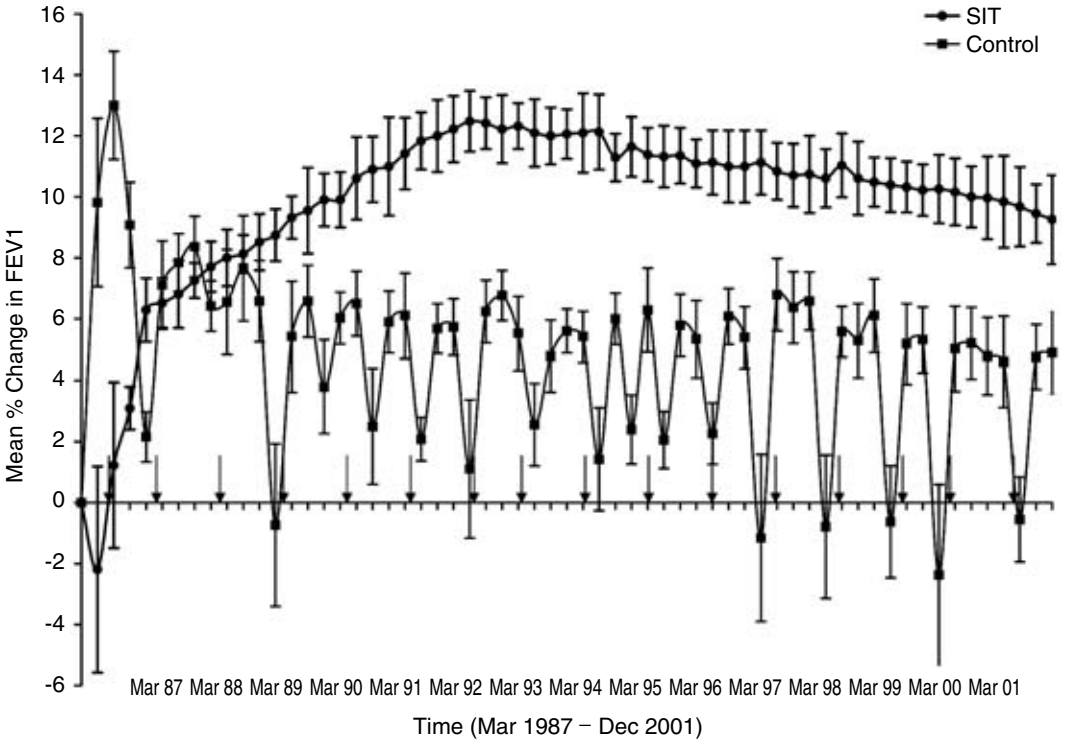

Fig. 1 Percentage change and variation in FEV_1 in the control (C) and specific immunotherapy (SIT) groups over a period of 15 years

mately 40 bioequivalent allergy units (BAU/ml) to start with[9] a maximum of 8000 BAU/ml during the maintenance phase, which would be designated as "high dose." All the instructions provided by the manufacturer (Alcit India Pvt. Ltd.) were carefully followed. Side effects of SIT (local and systemic) if any, were observed and carefully recorded at each consultation. Between January 1, 1987 and December 31, 2001, while the study was ongoing, symptom scores and FEV1 of each patient were recorded once every 3 months on the first day of March, June, September and December.

Symptom Scores

Symptom scores were assessed on a visual analogue scale (VAS) from 0 to 10, where "0" indicated worsening or no improvement and 10 indicated maximal improvement. While assessing symptom scores, patients were instructed to make a global evaluation, including frequency and severity of symptoms, presence of other complaints such as cough and phlegm and improvement in quality of life.

Since symptom scores were evaluated for a lengthy 15 year period, the possibility of patients forgetting their initial global symptom severity and intensity was kept in mind. Consequently during the symptom score evaluation period every attempt was made to jog the patients memory, re-live symptom severity at the beginning of the study, compare it with the status on evaluation day and then decide on the current symptom score.

Spirometry

FEV 1 values obtained through spirometry were noted and the percentage change in FEV1 (PCFEV1) was calculated at each visit, taking the FEV1 at the beginning of the study as the baseline value. Although this was an open trial, in order to eliminate bias, the clinic secretaries recorded symptom scores and the clinic physician conducted spirometry. Clinic secretaries were strictly instructed not to discuss with patients their mode of treatment. Also, patients from both groups were assigned to different days for clinic visits (even dates for the SIT group and odd dates for the control group) so as to ensure that no patients from one group would meet patients from the other group during the course of this study.

Rescue Medication Records

Each patient was instructed to keep a careful record of the number of doses of rescue salbutamol used. Patients were asked to report back to the clinic if they had any uncontrolled symptoms or clarifications. Patients not responding to salbutamol MDI were asked to report to the clinic immediately and were prescribed a short course of oral prednisolone, begin-

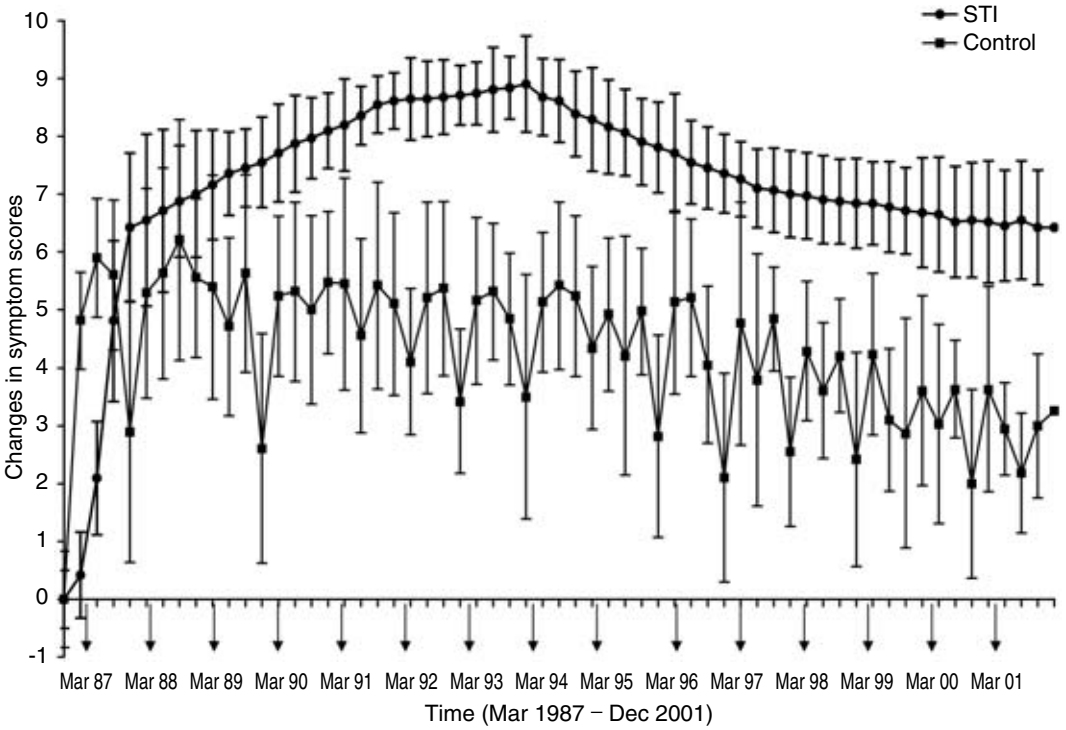

Fig. 2 Percentage change and variation in symptom scores in the control (C) and specific immunotherapy (SIT) groups over a period of 15 years

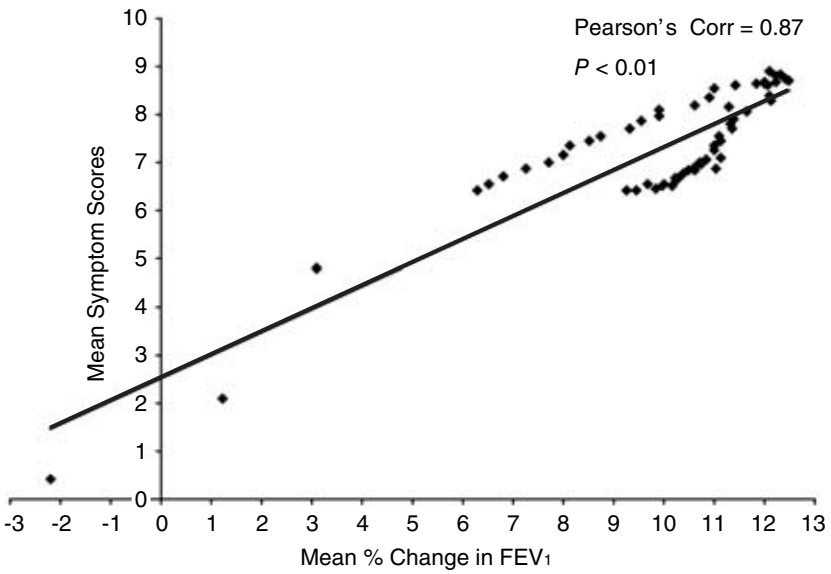

Fig. 3 Correlation between mean % change in FEV_1 and mean symptom scores in the specific immunotherapy (SIT) group

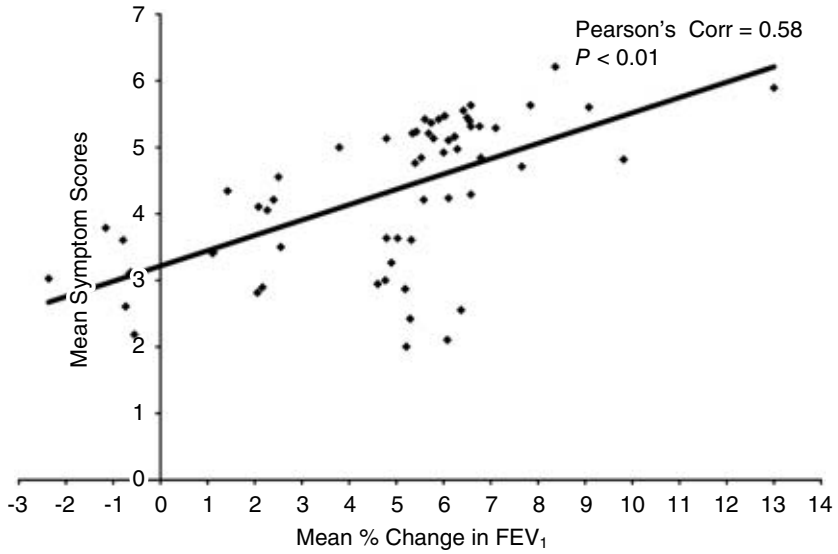

Fig. 4 Correlation between mean % change in FEV_1 and mean symptom scores in the control group

ning with 30 mg per day and tapered off within 3 weeks.

Skin Prick Tests

SPT with *D. farinae* was repeated in all 85 patients before the beginning of the study (December 1986), on discontinuation of SIT (January 1992) and on completion of the study (January 2002).

Statistical Analysis

Analysis of the correlation coefficient was calculated using Pearson's test. The Mann Whitney test and Wilcoxon Rank Sum test were used to compare the symptom scores. PCFEV1 and SPT wheal sizes in the two groups with p values < 0.05 were considered statistically significant. Area under the curve (AUC) was used to compare the overall effect of SIT with the control group over the entire duration of the 15 year period. The SPSS statistical package was used to predict the maximum possible period of benefit obtained with SIT.

RESULTS

Data obtained from this study showed that patients in the control group suffered from their disease for 1 to 6 years (mean duration-2 years 7 months) whereas those in the SIT group suffered for 1 to 7 years (mean duration-3 years 5 months).

Total serum IgE levels were in the range of 426 to 978 IU/ml. (mean-581 IU/ml.) in the control group and 488 to 1007 IU/ml (mean - 602 IU/ml.) in the SIT group.

Based on the International Consensus Report,[7] all 69 cases were classified as "moderately severe asthma." Control group patients had FEV1.0 ranging from 68% to 76% of predicted normal values (mean-71%) while those in the SIT group had FEV1.0 ranging from 66% to 70% (mean-70%).

The baseline data in this study revealed that the SIT and Control groups were well matched with regard to age, sex, disease period, total serum IgE levels and FEV1.0 (p< 0.05). This close match occurred despite proper randomization and without any attempt at stratification.

The results obtained from this study are shown in Figures 1–4.

Both the PCFEV1 and the symptom scores were evaluated for each time point over a period of 15 years for both SIT and control group. Data were expressed as means +/- standard deviation (SD). Patients receiving SIT showed less variability in SD whereas patients in the control group showed a large variation over the 15-year period (Fig. 2).

Patients in the control group showed wide deviations in mean symptom scores (range 2.60 to 6.21) and in PCFEV1 (varying up to 7%) during the study period. However, the SIT group showed a marked improvement through December 1987, a steady increase until December 1993, followed by a gradual decline until December 2001 (Fig. 2).

Pearson correlations between mean PCFEV1 and mean symptom scores (Figs. 3, 4) showed "a highly significant correlation" in the SIT group (r = 0.87, p < 0.01) and "a significant correlation" in the control group (r = 0.58, p < 0.01).

The Mann-Whitney Test was performed for symptom scores. The null hypotheses of no difference between patients receiving SIT and control group was

Table 1 AREA UNDER THE CURVE (AUC)

Parameter	Group	1987 to 1991	1992 to 2001	1987 to 2001	"p" values
% change in FEV1.0 (PCFEV1)	SIT	159.72	409.38	569.10	$p < 0.05$
	Control	122.78	155.33	278.11	
Symptom Scores	SIT	139.85	277.73	417.58	$p < 0.05$
	Control	101.43	145.78	247.21	

rejected. There was a statistically significant difference between the two groups ($p < 0.01$) with statistically significant higher symptom scores in the SIT group.

Area under the curve (AUC) was estimated by means of linear interpolation using the trapezoidal rule (EquivTest, version 2.0, Solutions Ltd., Republic of Ireland). AUC was calculated for both PCFEV1 and symptom scores in both groups for the entire 15-year period (1987 to 2001) and also separately for the period during which SIT was administered (1987 to 1991) and the follow-up period (1992 to 2001)(Table 1).For all 3 periods, the AUC analysis concluded that the AUC is significantly higher for the SIT group for both PCFEV1 and symptom scores ($p < 0.05$).

The two sample Wilcoxon Rank Sum Test and confidence intervals (CI) for symptom scores and PCFEV1 for March 1987 when compared with December 2001 for the SIT group showed a statistically significant difference ($p < 0.05$) and significantly higher scores for December 2001.

The data obtained from this study was applied to the SPSS version 11.0 statistical package in an attempt to determine the maximum period of benefit following cessation of SIT. The "curve fit method", predicted that symptom scores and PCFEV1 would drop to zero in December 2014, which is after a duration of 28 years following initiation of the study (in January 1987).

The two-sample Wilcoxon Rank Sum Test was applied to the skin prick test data which revealed no significant differences in wheal sizes when the 3 readings (1986, 1992 and 2002) were compared to each other in both the SIT and control groups.

Although side effects were not included in the study plan, it is pertinent to note here that there were no systemic reactions in the SIT group. There were however, 20 episodes of small local reactions (<4 cm in diameter) at the site of injection, none of which required therapeutic intervention.

The records maintained by patients revealed that the control group inhaled a total of 61,400 puffs of salbutamol (approximately 307 MDI's) during the first year of this study as rescue medication. During the same period the SIT group inhaled 8,600 puffs (or approximately 43 MDI's). The difference therefore, between the two groups with regards to rescue medication, is stark. However, no reliable data could be obtained for the rest of the study due to inaccurate recording of MDI usage by patients in both groups.

None of the 31 patients in the SIT group needed prednisolone during the 15-year study period. However, there were a total of 347 occasions when prednisolone was administered to patients from the control group ; thus on an average each control group patient required prednisolone 9 times during the study.

DISCUSSION

The end points used in this study, viz. PCFEV1 and symptom scores are accepted as two of the most convenient methods of monitoring the clinical efficacy of SIT. Bronchial hyper reactivity (BHR) was not considered as a parameter in this study since it has yielded conflicting results in patients undergoing SIT. Of the eight studies measuring BHR before and after SIT, only one showed a decrease in BHR, but the remaining seven showed no change.[9]

In addition there have been conflicting results with regard to changes in skin reactivity following SIT. In 13 out of 30 beneficial studies with SIT, four showed no change and nine demonstrated decreased skin test reactivity.[10] Furthermore, the present study confirms that test reactivity is not a reliable end point for studying the efficacy of SIT.

A number of studies have studied the efficacy of SIT in asthma and/or rhinitis over periods varying from 1 to 6 years using house dust mite, tree and grass pollen, fungi (Alternaria) and animal danders (cat and/or dog).[11-21] Only one study observed the effects of SIT over a period of 14 years.[22] However, that study did not use any of the usual end points viz, symptom scores, PCFEV1, SPT wheal size or bronchial hyperresponsiveness. Indeed, this same study did not discuss the details of statistical analysis.

The present study has shown a statistically significant improvement in end points in the SIT group, which persisted for a decade after cessation of SIT and using statistical projection would be expected to last for approximately 13 years after completion of the study (or for a total of 23 years following discontinuation of SIT). This study concludes that contrary to all current skepticism, SIT indeed has a long lasting beneficial role in BA. In sum, SIT could therefore be considered a truly disease modifying drug (DMD).

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