

Sublingual Immunotherapy with House Dust Extract for House Dust-Mite Allergic Rhinitis in Children

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ABSTRACT

Background: House dust extract is used in conventional immunotherapy for house dust-mite (HDM) allergic rhinitis in Japan. However, an alternative administration route is desired. The aims of the present double blind, placebo-controlled trial were to evaluate the therapeutic efficacy and safety of sublingual immunotherapy (SLIT) with house dust extract in pediatric patients with HDM allergic rhinitis.

Methods: The study population comprised 31 subjects (21 males and 10 females) aged from 7 to 15 years old. Twenty patients (the active group) received house dust extract and 11 received placebo via sublingual administration. Extract or placebo (1 ml) was administered at 10-fold dilution once weekly for 40 weeks. During the study period, the subjects recorded their daily nasal symptoms and use (dose and frequency) of other medications in a nasal allergy diary.

Results: The symptom scores in the active group began to decrease about 24 weeks after initiation of treatment and significant differences between the active and placebo groups were observed after 30 weeks. The average scores for the last four weeks of the study were significantly lower than those for the first four weeks in the active group but not in the placebo group. The only local adverse effect was a bitter taste reported by one patient. There were no other local or systemic adverse effects associated with SLIT.

Conclusions: Our results suggest that SLIT with house dust extract for more than 30 weeks is safe and effective treatment for HDM allergic rhinitis in children.

KEY WORDS

children, double blind, house dust extract, house dust-mite allergic rhinitis, placebo-controlled trial, sublingual immunotherapy

INTRODUCTION

An increased prevalence of allergic rhinitis has been found worldwide^{1,2} and the onset age has decreased in pediatric patients.² Once allergic rhinitis develops in childhood, the disease does not remit easily³ and may impair quality of life and school performance for many years.^{4,5} Current therapy for allergic rhinitis includes allergen avoidance, symptomatic medication,

and immunotherapy. Conventional allergen-specific immunotherapy via the subcutaneous route (SCIT) is effective for changing the natural course of allergic rhinitis and has long-term effects.⁶⁻¹¹ However, an alternative administration route is still required since the SCIT approach requires multiple injections and frequent visits to a physician's office, and can have severe systemic adverse effects.¹² A safer and simpler approach is particularly important for pediatric pa-

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Table 1 Dose and dosing frequency

	Week 1	Week 2	Week 3	Week 4
	1000 fold	100 fold	10 fold	10 fold
Day 1	0.2 ml	0.2 ml	0.2 ml	1.0 ml
Day 2	0.4 ml	0.4 ml	0.4 ml	
Day 3	0.6 ml	0.6 ml	0.6 ml	
Day 4	0.8 ml	0.8 ml	0.8 ml	
Day 5	1.0 ml	1.0 ml	1.0 ml	
Day 6				
Day 7				

tients.

Sublingual allergen-specific immunotherapy (SLIT) may offer a safe and effective alternative administration route and has attracted particular attention in Europe. The house dust mite (HDM) is the major allergen in pediatric patients and several randomized controlled trials of HDM in children have been reported.¹³⁻¹⁶ Bahçeciler *et al.*¹³ treated 15 pediatric patients with HDM extract for 6 months and showed that the mean daily doses of intranasal steroids decreased in these patients. Ippoliti *et al.*¹⁴ similarly treated 86 pediatric patients for 6 months and found a significant reduction in rhinitis scores in the treatment group compared with patients who received a placebo.

In Japan, SCIT for HDM allergic rhinitis has been conducted with house dust extract but not with mite extract for more than 40 years and has been shown to be effective.¹⁷ Although house dust extract contains not only mite allergens but also other antigens, such as cockroach, moth and mold, the Japanese Ministry of Health, Labour, and Welfare has only approved the use of house dust extract for immunotherapy. The mite extract widely used in western countries is not available in Japan. One milliliter of the house dust extract contains about 7 µg of Der f 1, one of the major allergens of *Dermatophagoides farinae*. The concentrations of other allergens have not been determined. To evaluate the efficacy of SLIT, a double-blind placebo controlled study was conducted in pediatric patients with HDM allergic rhinitis using the house dust extract used in Japan.

METHODS

SUBJECTS

The study population comprised 31 subjects (21 males and 10 females) ranging in age from 7 to 15 years old and living in Chiba, Hokkaido, or Akita. The subjects had a clinical history of HDM allergic rhinitis, but were otherwise healthy. Diagnosis of HDM allergic rhinitis was based on clinical history, positive allergen-specific skin tests (wheal diameter ≥ 10 mm) to house dust extract (Torii Pharmaceutical, Tokyo, Japan), and a serum house dust mite-specific IgE score ≥ 2 on the CAP-radioallergosorbent test (CAP-

RAST, SRL Inc., Tokyo, Japan). Patients who had been treated with any allergen-specific immunotherapy (including with house dust) and those with severe or poorly controlled asthma were excluded. The study was conducted at Chiba University Hospital, Chiba Children's Hospital, Hokkaido University Hospital, and Akita University Hospital, in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice and the Declaration of Helsinki (2000 revision). The protocol was approved by the Ethics Committee of each hospital, and written informed consent was obtained from each subject prior to their participation in the study.

HOUSE DUST EXTRACT

Extracts of house dust (Torii Pharmaceutical: lot number; ASCY) were used in the study. This extract contained 5 µg/ml of Der f 1.

STUDY PROTOCOL

The study was performed as a placebo-controlled, double-blinded trial. The subjects were randomly allocated into two groups based on a table of random numbers produced by the Department of Pharmacy at Chiba University Hospital. An administrator who was not directly involved in the study was responsible for group allocation. The patients were randomly placed into active (treatment) and placebo groups at a ratio of 2 : 1. A group allocation number was given to each patient. This information was retained by the administrator and a member of the ethical committee who was also not directly involved in the study. The numbers were accessed with a key after completion of the study.

The active group (20 patients) received house dust extract and the placebo group (11 patients) received placebo by sublingual administration using the spit method (Table 1). Following a week for washout before treatment (Week 0), the dose was escalated over a period of 3 weeks by administration of an increasing number of extract or placebo drops at three concentrations. Patients received increasing doses from each vial, beginning with 0.2 ml from a 1000-fold diluted vial, and increasing by 0.2 ml per day over 5 days. The vaccine was taken sublingually, kept for 2 min without retention reagent, and then spit out. The procedure was then repeated with each vial until the maximum dose (1.0 ml of a 10-fold diluted vial) was reached, as shown in Table 1. The safety of daily SLIT administration has been shown, but weekly administration was used in this study to minimize the possibility of serious adverse events. The safety of weekly administration was confirmed in our previous study in patients with Japanese cedar pollinosis.¹⁸ The maintenance dose was about 20 times higher than that used in conventional subcutaneous immunotherapy. Administration was started in November/December 2006 and the study was completed at the

Table 2 Severity of nasal symptoms

Parameter	Severity				
	++++	+++	++	+	-
Paroxysmal sneezing (times/day)	≥21	11-21	6-10	1-5	0
Runny nose (Nose blowing frequency; times/day)	≥21	11-21	6-10	1-5	0
Nasal congestion	Complete congestion, all day	Very severe nasal congestion with frequent oral breathing	Severe nasal congestion with occasional oral breathing	No oral breathing but nasal congestion	None

Adapted from the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2009.

Table 3 Baseline characteristics of the patients

	Active Group <i>n</i> = 19	Placebo Group <i>n</i> = 9
Mean age, years (SD)	9.4 (2.2)	9.6 (2.5)
Female sex, <i>n</i> (%)	6 (31.6)	2 (22.2)
Mite RAST score, mean (SD)	4.7 (1.2)	5.3 (0.8)
Mean duration of HDM allergic rhinitis, years (SD)	5.9 (2.9)	5.3 (2.1)
Additional allergic disease, <i>n</i> (%)		
Current bronchial asthma	8 (42.1)	7 (77.8)
Current atopic dermatitis	5 (26.3)	2 (22.2)
History of atopic dermatitis	1 (5.3)	0 (0)
Current Japanese cedar pollinosis	1 (5.3)	1 (11.1)

end of October 2007. Patients visited the hospital just after the period of dose escalation and once every three months thereafter. At each visit, physicians checked intranasal findings, nasal allergy diaries and adverse events.

SYMPTOM SCORING

During the study period the subjects recorded their daily nasal symptoms and use (dose and frequency) of other medications in a nasal allergy diary. Symptom, medication and symptom-medication scores were obtained from the diary records using the following criteria based on a modified Okuda classification (Table 2).^{19,20} For nasal symptoms, the severity of paroxysmal sneezing (number of sneezes per day), runny nose (number of times blowing the nose per day) and nasal congestion were evaluated on a five-point scale (0-4): 0, no sensation; 1, mild; 2, moderate; 3, severe; and 4, extremely severe. Episodes of sneezing and nose blowing (rhinorrhoea) per day were rated from 0 to 4: 0, none; 1, 1-5 episodes; 2, 6-10 episodes; 3, 11-20 episodes; and 4, >21 episodes. The daily total nasal symptom score was expressed as the highest score for nasal symptoms. Medication was recorded based on drug characteristics and duration of use, using the following codes²¹: 1, anti-histamines, mast cell stabilizers and vasoconstrictors; 2, topical, ocular or nasal steroids. The medication score and

symptom-medication score (medication + symptom scores) were calculated for each patient. The symptom and symptom-medication scores were used as the primary outcome parameter and other criteria were used as secondary outcome parameters.

STATISTICAL ANALYSIS

After completion of the study, clinical and laboratory data were analyzed by a biostatistician who had previously not been involved in the trial. After the analysis was complete, the allocation identification numbers for the active and placebo groups were accessed. Data analysis was performed with two-tailed tests at a significance level of 5%, using a chi-square test, a Mann-Whitney U test and a Wilcoxon signed-rank test in SAS v. 8.02 (Cary, NC, USA).

RESULTS

SUBJECTS

Three subjects were excluded from analysis because of incomplete allergy diaries. None were excluded due to adverse effects. Data were analyzed for the remaining 28 subjects, who showed full compliance with the study protocol (Table 3). These subjects included 19 in the active group (mean age 9.4 years old, mite RAST score 4.7, duration of HDM allergic rhinitis 5.9 years) and 9 in the placebo group (mean age 9.6 years, mite RAST score 5.3, duration of HDM

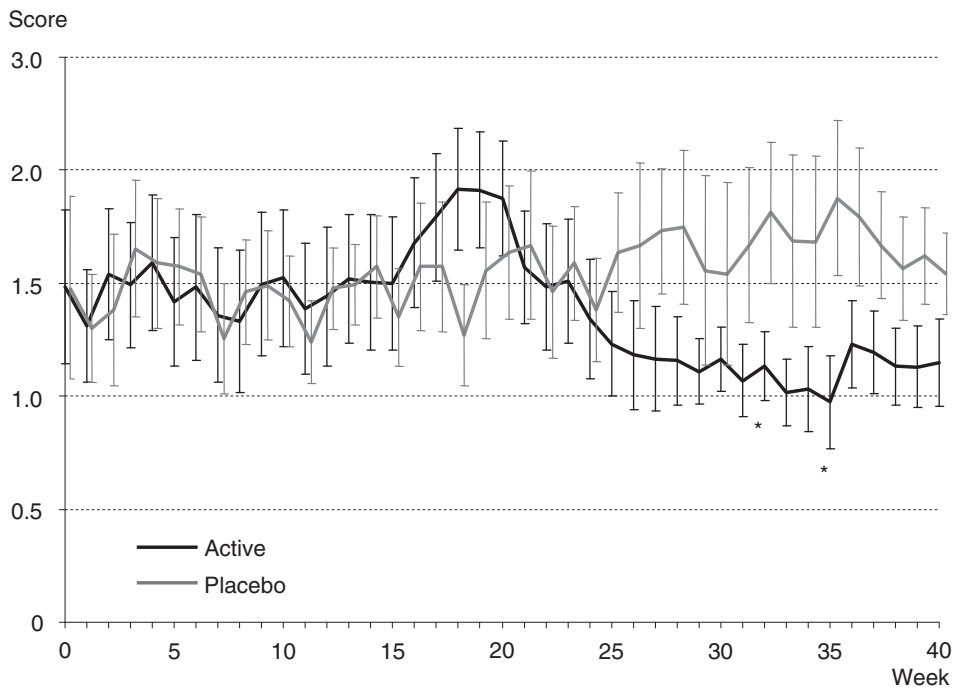


Fig. 1 The mean scores for paroxysmal sneezing and runny nose in the active group decreased after week 24 and were significantly lower than those in the placebo group in 32 and 35. * $p < 0.05$ (vs. placebo group, Mann-Whitney U test).

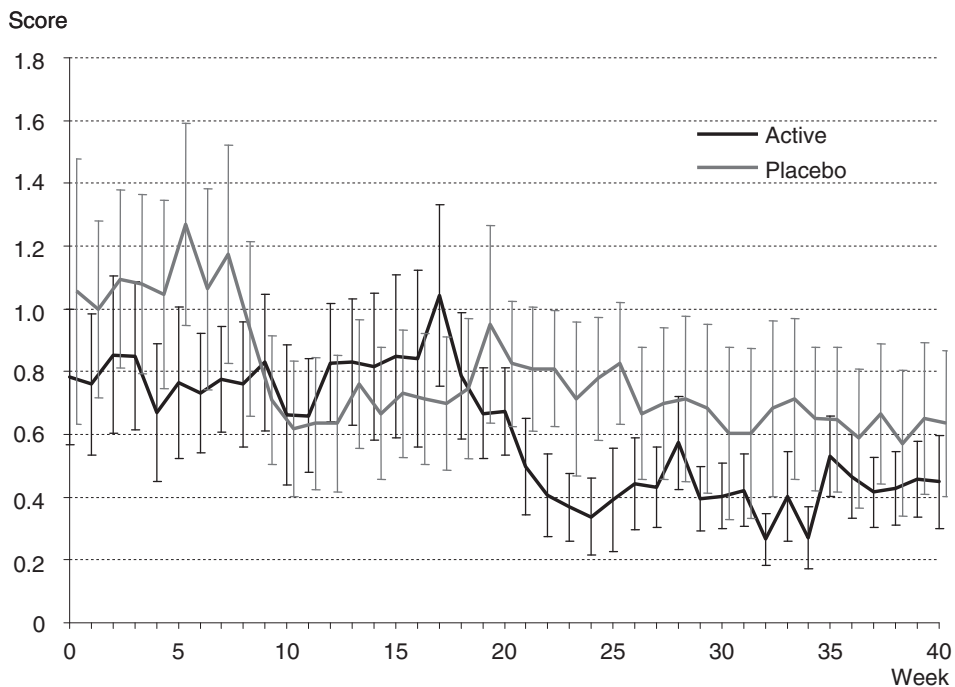


Fig. 2 The mean score for nasal congestion in the active group decreased after week 20.

allergic rhinitis 5.3 years). There were no significant differences in age, sex, mite RAST score and duration of HDM allergic rhinitis between these two groups. The active group included 8 patients with current

asthma, 5 with current atopic dermatitis, and 1 with a history of current atopic dermatitis. The placebo group included 7 patients with current asthma and 2 with current atopic dermatitis. Each group had 1 pa-

SLIT for Allergic Rhinitis in Children

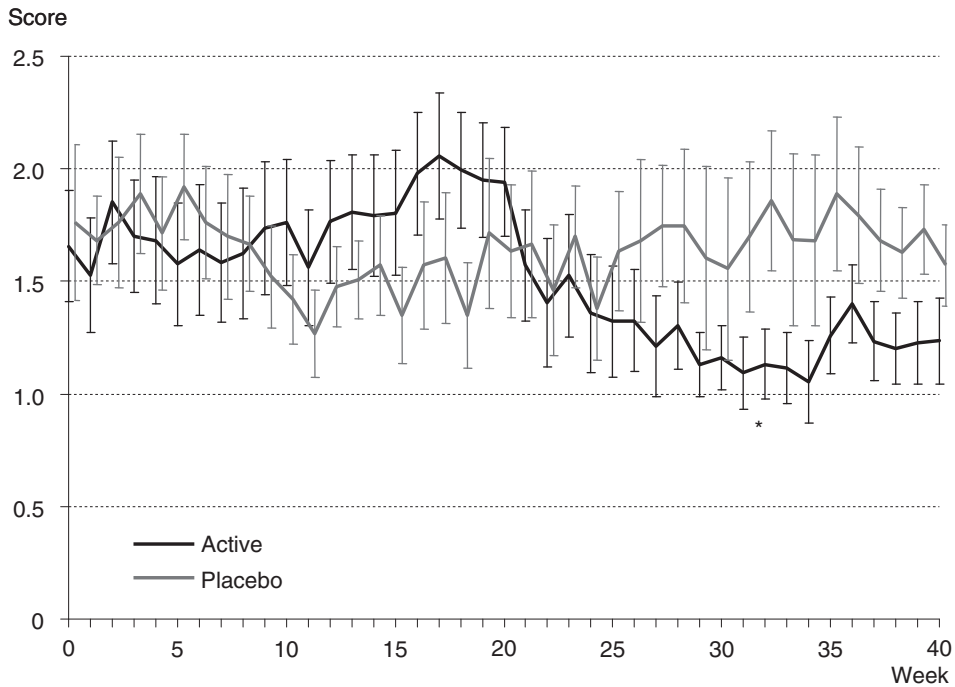


Fig. 3 Symptom scores in the active group decreased after week 24 and were significantly lower than that in the placebo group in week 32. * $p < 0.05$ (vs. placebo group, Mann-Whitney U test).

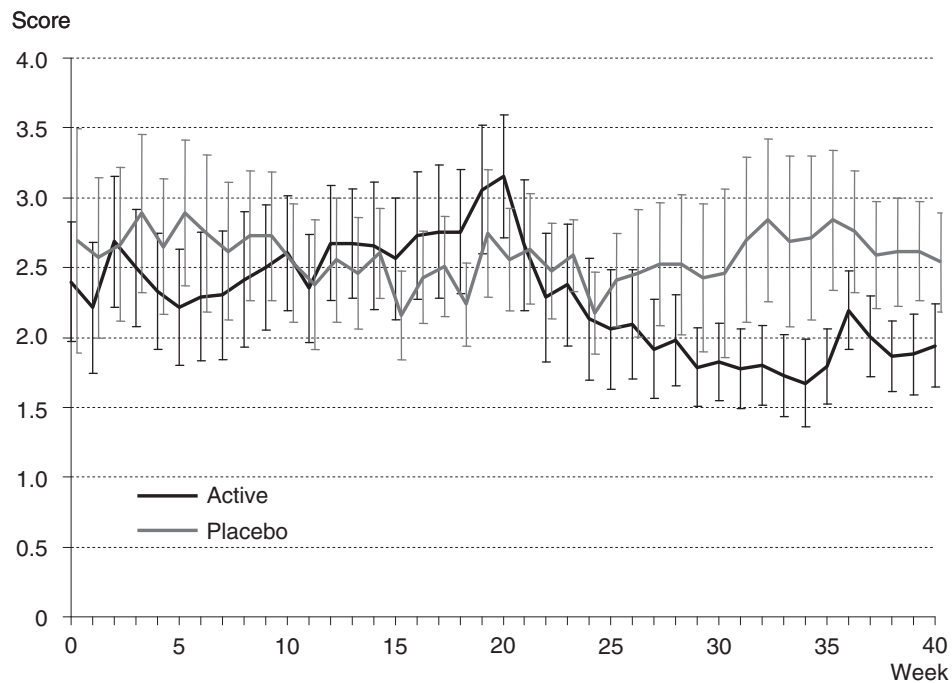


Fig. 4 The mean symptom-medication score decreased after week 24 in the active group.

tient with current Japanese cedar pollinosis. The rates and severities of the additional allergic diseases did not differ significantly between the two groups.

NASAL SYMPTOMS SCORES

The mean nasal symptom scores for each week of the study are shown in Figure 1, 2. The mean higher score for paroxysmal sneezing or runny nose (Fig. 1)

did not differ between the active and placebo groups until week 24. After this time, this score decreased for the active group but not for the placebo group, and the mean scores were significantly lower in the active group in weeks 32 and 35. The mean nasal congestion scores (Fig. 2) changed randomly in both groups until week 20, but decreased thereafter in the active group.

SYMPTOM AND SYMPTOM-MEDICATION SCORES

The mean symptom and symptom-medication scores for each week of the study are shown in Figure 3, 4. These scores showed similar tendencies. Both were almost constant throughout the study in the placebo group, but decreased after week 24 in the active group. The mean symptom scores were significantly lower in the active group in week 32. A comparison of the average scores for week 0-3 (a week of washout before treatment and the first 3 weeks of treatment) with those for weeks 37-40 (the final 4 weeks of treatment) is shown in Figure 5. The average symptom score for weeks 37-40 was significantly lower than that for weeks 0-3 in the active group, while there was no significant difference in the placebo group. The average symptom-medication score for weeks 37-40 was also lower than that for weeks 0-3 in the active group, but the difference was not significant. In the placebo group, the average symptom-medication score did not decrease significantly over the study period.

IMPROVEMENT OF SYMPTOMS

The average symptom score for weeks 37-40 was compared with the baseline score (the average score for weeks 0-3) in each patient. A decrease of more than 1 point was taken to indicate improvement of symptoms, and this was found in 33% of patients in the active group but in 0% in the placebo group (Fig. 6). Similarly, the symptom scores one year after the end of the trial were compared with those at baseline. This showed improved symptoms in 16% of patients in the active group, but in 0% in the placebo group.

EFFECT ON OTHER ALLERGIC DISEASES

Of the 8 and 7 patients with asthma in the active and placebo groups, respectively, the frequency of asthma attacks after the trial was reduced in 2 and unchanged in 6 in the active group, and was reduced in 3 and unchanged in 4 in the placebo group. Of the 5 and 2 patients with atopic dermatitis in the active and placebo groups, respectively, improvement of symptoms occurred in 1 patient in the active group. The other 6 patients showed no change through the study. There was no significant difference between the active group and the placebo group in the therapeutic effects on asthma and atopic dermatitis.

ADVERSE EFFECTS

One patient in the active group reported a bitter taste. There were no other local adverse effects and no severe systemic adverse effects related to the treatment.

DISCUSSION

HDM is the most common allergen in pediatric patients with allergic rhinitis. Natural remission of the disease is rare in childhood and the condition carries over to adulthood in most patients. Allergen-specific SCIT is the only current therapy that can alter the natural course, but the treatment has practical inconveniences. SLIT has been proposed as an effective alternative, but the efficacy of SLIT in pediatric HDM allergic rhinitis has yet to be shown based on recent reviews.²²⁻²⁴ Therefore, we examined the therapeutic effect of SLIT with house dust extract on pediatric HDM allergic rhinitis over a period of 10 months in a placebo-controlled study. This house dust extract is only available in Japan and contains moth, cockroach and mold antigens, in addition to mite. Except for Der f, the concentrations of these antigens are unknown. The active group had significantly lower symptom scores compared to the placebo group after treatment for 30 weeks, and the mean symptom score in the active group in the last four weeks of the study was significantly lower than that in the first four weeks.

The decrease in the symptom-medication score was not significant, but the medication score may not reflect the exact quantity of rescue medicines for allergic rhinitis, since more than half of the patients had asthma or atopic dermatitis. To evaluate the efficacy of SLIT for asthma and atopic dermatitis, we chose criteria that did not exclude these complications. Of the 15 patients with asthma, 2 in the active group and 3 in the placebo group had a decreased number of attacks in the treatment period. Of the 6 with atopic dermatitis, only 1 patient in the active group showed improvement of symptoms. Therefore, the effects of SLIT on asthma and atopic dermatitis were unclear.

The results for nasal symptoms obtained in this study were comparable with those in randomized studies using standardized mite extracts, based on meta-analysis by Penagos²³ and Calamita.²⁵ One year after treatment, about half of the patients in the active group, but none in the placebo group, had improved nasal symptoms compared to the start of treatment. To obtain long-term effects, a longer treatment period may be necessary. The doses of allergen extract used in this study were about 20 times higher than those used in conventional SCIT in Japan. However, recent results of SLIT studies for pollinosis have recommended treatment for more than 18 months with doses of allergens of more than 100 µg. Further comparative studies are needed to assess the ideal doses, temporal intervals, and vehicles for administration.

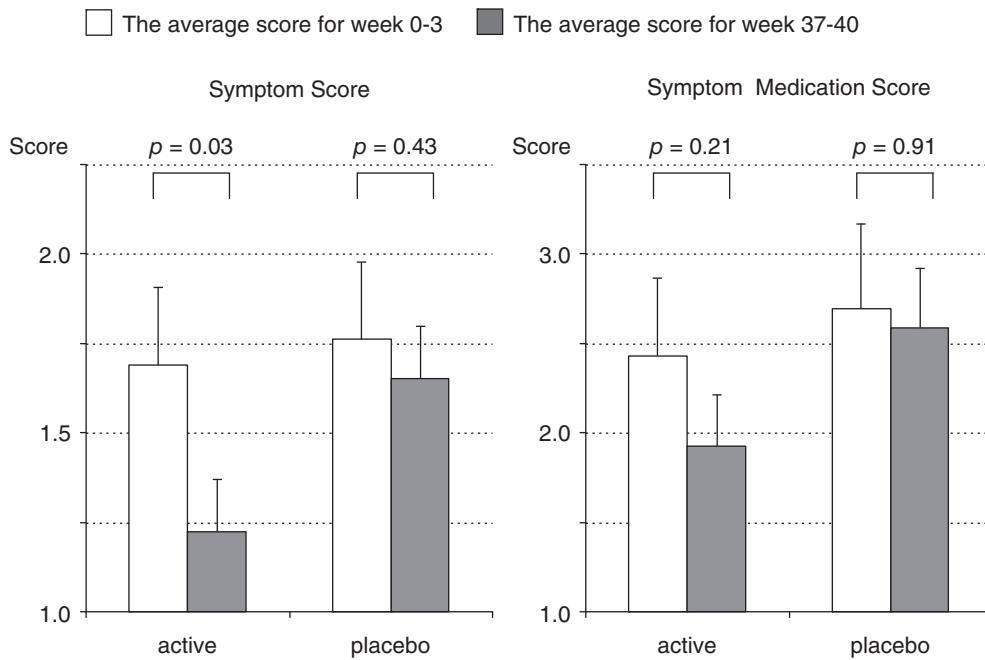


Fig. 5 The average symptom score for weeks 37-40 (the final 4 weeks of the study) was significantly lower than that for weeks 0-3 (a week of washout before treatment and the first 3 weeks of treatment) in the active group, whereas there was no significant difference in the placebo group. *p*: Wilcoxon signed-rank test.

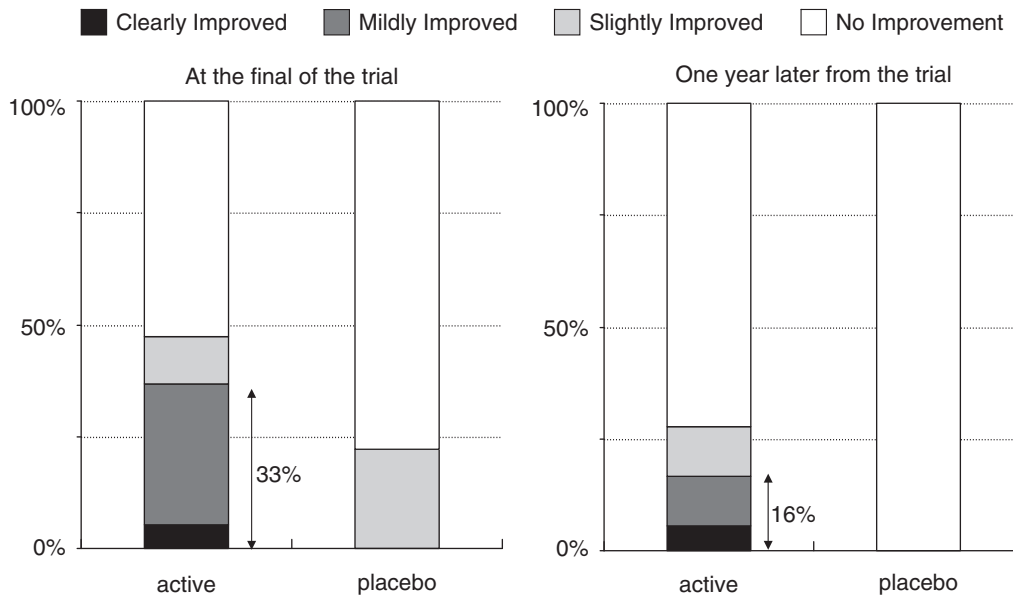


Fig. 6 Based on changes in symptom scores, improvement of symptoms was found in 33% of patients in the active group but in 0% in the placebo group at the end of the trial. At one year after the end of the trial, improvement was found in 16% of patients in the active group but in 0% in the placebo group.

Although the current study is preliminary, the results are encouraging and suggest a need for a new study that includes a comparison of the effects of house dust extract with those of a standardized mite extract.

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