

Original article

Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose–response study

Background: The effect of specific immunotherapy (SIT) on eczema in atopic dermatitis is not known. Therefore, a multi-centre, randomized dose–response trial, double-blind with respect to the efficacy of a biologically standardized depot house dust mite preparation was performed.

Methods: Eighty-nine adults with a chronic course of atopic dermatitis, SCORAD ≥ 40 and allergic sensitization to house dust mites [CAP-FEIA ≥ 3] were included, of whom 51 completed the study. Subcutaneous SIT with a house dust mite preparation (*Dermatophagoides pteronyssinus/D. farinae*) applying maintenance doses of 20, 2000 and 20 000 SQ-U in weekly intervals for 1 year. The main outcome measures addressed the change of the SCORAD as average of the values after 9 and 12 months of SIT in comparison with the value at baseline.

Results: The SCORAD declined in the three dose groups in a dose-dependent manner ($P = 0.0368$, Jonckheere–Terpstra test) and was significantly lower in the two high-dose groups (2000, 20000 SQ-U) compared with the low-dose group of 20 SQ-U ($P = 0.0379$, U -test) after 1 year of SIT. The use of topical corticosteroids was significantly reduced with higher doses ($P = 0.0007$, Mantel–Haenszel chi-square test).

Conclusions: Allergen-SIT for 1 year with a house dust mite preparation is able to improve the eczema in patients with atopic dermatitis who are sensitized to house dust mite allergens and reduces the need for topical corticosteroids. SIT may be valuable in the treatment of this chronic skin disease.

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Sensitization to inhalant allergens such as house dust mite (HDM) allergens, detectable with specific IgE tests, is very common in adolescent and adult patients suffering from atopic dermatitis (AD) (1).

A T-cell-mediated reaction is critical in the worsening of eczema, which can be triggered by the epicutaneous application of HDM allergens in sensitized patients (2, 3). HDM allergens penetrate the skin where they are trapped via specific IgE on high-affinity Fc-receptors on Langerhans cells. Langerhans cells may subsequently present the allergens to T lymphocytes, leading to specific T-cell proliferation and eczema.

A causal therapy for AD is not available, and the complexity of the disease leads to different approaches to treatment. Subcutaneous immunotherapy (SIT) inhibits the progress of IgE-mediated allergic diseases. However,

little information on the effects of SIT in AD has been published. Most findings have been derived from open studies (4–9), or the investigations were not based on established protocols of SIT (10, 11). We tested the hypothesis that 1 year of SIT would improve eczema in patients with AD in a dose-dependent manner and evaluated the effect of SIT on corticosteroid and antihistamine use.

Methods

Study design

We conducted a multi-centre, randomized trial, double-blind with respect to efficacy and single-blind with respect to safety in seven centres, to investigate the dose–response of SIT with mite allergens (ALK-depot SQ) in AD patients, using doses for maintenance

treatment of 20, 2000 and 20 000 SQ-U for 1 year. The study was conducted according to the Good Clinical Practice guidelines (ICH-GCP) and was approved by the ethical committees of all study centres.

Participants

Patients between 18 and 55 years of age with chronic AD who showed IgE-mediated sensitization against HDM verified by CAP-FEIA (Pharmacia, Freiburg, Germany) with a CAP class ≥ 3 and a SCORAD (12) value ≥ 40 were eligible for the trial.

We excluded patients with allergic bronchial asthma requiring systemic steroids, patients treated with UV radiation or with group 4 topical corticosteroids (European classification) or systemically with corticosteroids or immunosuppressant agents in the 4 weeks before the start of the study, and those who had a history of immunotherapy with HDM within the last 3 years.

Treatment

Patients were randomized by the biometrician into three dose groups for treatment with SIT (ALK-depot SQ *Dermatophagoides pteronyssinus*/D. *farinae*, ALK-SCHERAX, Hamburg, Germany; 100 000 SQ-U correspond to 4.9 μ g Der p 1 and 6.9 μ g Der f 1 mite major allergen) with a validated computer program with a block size of 6.

Patients in group 1 were treated with a constant dose of 20 SQ-U; patients in groups 2 and 3 with increasing doses starting from 20 SQ-U to maintenance doses of 2000 SQ-U (group 2) and 20 000 SQ-U (group 3). At the level of 200 and 2000 SQ-U during up-dosing, the dose was maintained for four injections (plateau phases) before further up-dosing. All injections were given at weekly intervals.

Masking and assessments

Patients were enrolled by an experienced dermatologist as a 'blind observer' who evaluated the SCORAD at the first and at all follow-up visits after 2, 4, 6, 9 and 12 months of treatment. The immunotherapy injections were administered by physicians aware of the allergen dose applied. Any reactions to the injections were seen and reported by the physician who administered the injections, and not by the blind observer. The blind observer was not allowed to communicate with the physician about patients, treatment, or study outcome. An appropriate volume of diluent was added to the active solution to ensure identical injection volumes for all injections in all three groups. HDM-specific and total IgE were measured at baseline and after 4 and 12 months of SIT, eosinophil cationic protein (ECP) was measured at each visit.

Emollients, topical corticosteroids up to European class 3 and cetirizine or loratadine were allowed for treatment during the study period. The condition of the skin and the use of drugs were documented daily by the patient.

Outcome measures

The primary outcome measure was the mean of the difference between the average of the SCORAD values after 9 and 12 months of SIT and baseline. For patients withdrawn prematurely, the last two SCORAD values were used to determine the primary outcome, or the score after 2 months was used if the SCORAD had been assessed only once on treatment. Secondary outcome measures were the change the use of topical corticosteroids and antihistamines between baseline and the last diary period, and the changes in IgE and ECP levels for the same period.

Analysis

The statistical analysis of changes from baseline in mean SCORAD values was performed in four steps: Groups 2 and 3 were compared with group 1, i.e. 'active immunotherapy' with 'active placebo', using the Mann-Whitney *U*-test (step 1). If step 1 showed statistical significance, groups 1, 2 and 3 were compared for a monotonous dose-response using the Jonckheere-Terpstra test (step 2). If step 2 showed statistical significance, group 3 was compared with group 1 using the *U*-test (step 3). If step 3 showed statistical significance, group 2 was compared with group 1 using the *U*-test (step 4).

The course of the SCORAD was analysed using analysis of covariance in the subgroup of completers. Further group comparisons of baseline characteristics and secondary study outcomes were carried out using analysis of variance, the Kruskal-Wallis test, chi-square test, Cochran-Armitage test and the Mantel-Haenszel chi-square test. The level of significance was $\alpha = 0.05$; all tests were two-tailed.

Results

Participant flow

We included 42 men and 47 women; 10 patients were excluded from efficacy analysis because they discontinued SIT in the first 8 weeks. The randomization successfully produced groups that were similar with respect to baseline characteristics (e.g. severity of eczema, degree of specific sensitization to HDM, perennial rhinitis).

The flow of patients is shown in Fig. 1. Fifty-one patients completed the study and were included in the SCORAD evaluation for the 1-year treatment period.

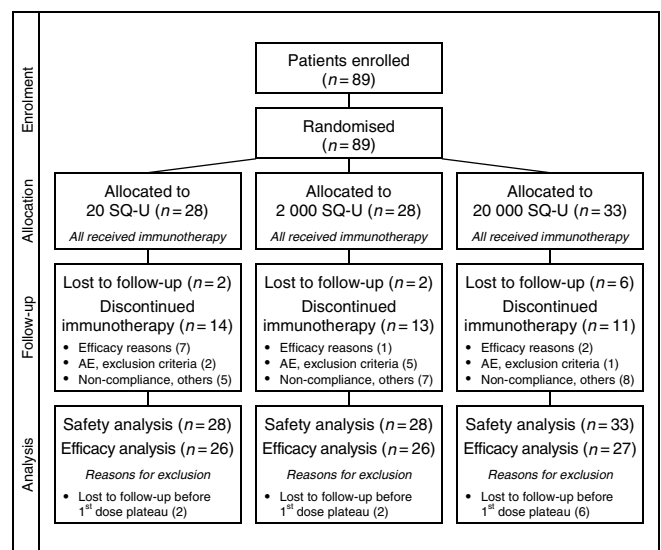


Figure 1. CONSORT diagram showing the flow of patients through the study.

Effect of SIT on eczema

The mean SCORAD decreased in all three study groups (Table 1). The difference between the two higher dose groups (2000 and 20 000 SQ-U) and the lowest dose group (20 SQ-U) was significant ($P < 0.05$), similar to the dose–response relationship throughout treatment ($P < 0.05$). The pair-wise comparison of the dose groups resulted in a significant difference in mean SCORAD between groups 3 and 1; the difference in the mean SCORAD between groups 2 and 1 was not significant.

Figure 2 shows changes in the mean SCORAD for completers. The improvement was significantly higher with 20 000 than 20 SQ-U from month 4 onwards.

Table 1. Changes in SCORAD upon specific immunotherapy (full analysis set)

Dosage (SQ-U)	n	Mean	95% CI	Median
Group 1: 20	26	−10.0	−15.8 to −4.2	−10.4
Group 2: 2000	26	−16.9	−22.7 to −11.2	−16.9
Group 3: 20 000	27	−19.0	−24.7 to −13.4	−20.3
Group 2 + 3: 2000 + 20 000	53	−18.0	−22.0 to −13.9	−18.7

Step	Comparison	Test	P-value
1	Group 2 + 3 vs 1	Mann–Whitney <i>U</i> -test	0.0379
2	Dose–response	Jonckheere–Terpstra test	0.0368
3	Group 3 vs 1	Mann–Whitney <i>U</i> -test	0.0399
4	Group 2 vs 1	Mann–Whitney <i>U</i> -test	0.1288

CI, confidence interval.

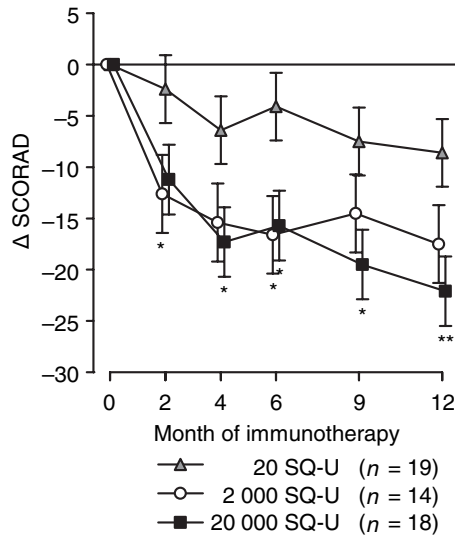


Figure 2. Differences from baseline (Δ) in SCORAD during 1-year specific immunotherapy with 20 SQ-U ($n = 19$), 2000 SQ-U ($n = 14$), and 20 000 SQ-U ($n = 18$) (mean \pm SEM; * $P < 0.05$, ** $P < 0.01$).

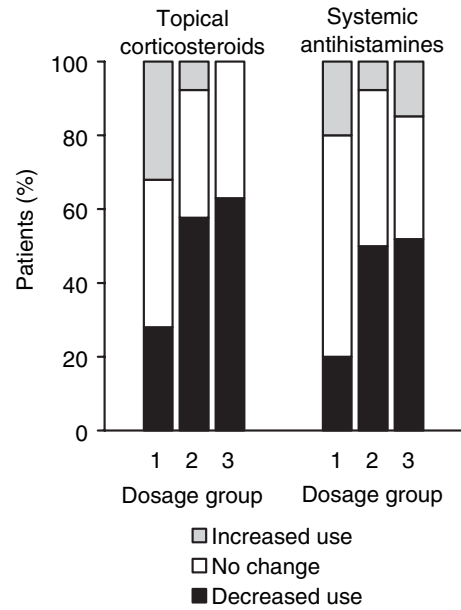


Figure 3. Changes in the use of topical corticosteroids ($P = 0.0007$) and systemic antihistamines ($P = 0.0594$) during specific immunotherapy (full analysis set, $n = 79$, Mantel–Haenszel chi-squared test).

Effect of SIT on the need for concomitant medication and on *ex vivo* serum parameters

The need for topical corticosteroids was significantly reduced with the higher doses of SIT ($P = 0.0007$, Mantel–Haenszel chi-square test) (Fig. 3). We observed a similar trend ($P = 0.0594$, Mantel–Haenszel chi-square test) in favour of groups 2 and 3 in the use of systemic antihistamines. No significant changes were observed in any of the treatment groups in specific and total IgE in ECP levels (data not shown).

Discussion

In this double-blind, dose–response study, SIT using a preparation of HDM was effective in reducing eczema in patients with chronic AD and allergic sensitization to HDM allergens in a dose-dependent manner. The improvement in the eczema was accompanied by a reduction in the use of topical corticosteroids.

We chose a treatment schedule with weekly injections and two plateaus during up-dosing for safety reasons and to keep the patients under close surveillance during the study because experience with SIT in the treatment of AD patients was limited when the study was designed: one double-blind, placebo-controlled and five observational studies have reported favourable outcomes (4–13). The double-blind, placebo-controlled study used allergen–antibody complexes (11) which have never subsequently been used in clinical practice. In a further controlled

study with negative results, allergens were inappropriately administered by the oral route (10).

Generally, the SIT was well tolerated in our study: systemic reactions (mild urticaria and itching) were documented after < 1% of injections. Of note, our study did not show that SIT results in deterioration of AD as reported sometimes by individual patients.

A high number of patients was lost to follow-up because of non-compliance with weekly injections. The analysis of the 51 completers showed no difference between the two higher dose groups up to month 6 of treatment. As treatment progressed further, however, a greater effect was seen with the highest dose (20 000 SQ-U), suggesting that a course of treatment with the standard maximum dose of 100 000 SQ-U at 4–8 weekly intervals may also be suitable for the treatment of AD.

In the active placebo dose group of 20 SQ-U, we observed a slight, continuous decline in mean SCORAD. This may reflect the placebo effect or – less probably – a slight therapeutic effect of SIT even with this low dose on AD.

We conclude that allergen SIT is effective in patients with AD sensitized to HDM allergens. SIT may be a useful approach to the treatment even of TH1-dominated skin lesions in AD (14, 15) which should be evaluated in further clinical studies.

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References

- Werfel T, Kapp A. Environmental and other major provocation factors in atopic dermatitis. *Allergy* 1998;**53**:731–739.
- Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TA. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;**16**:127–130.
- Sager N, Feldmann A, Schilling G, Kreitsch P, Neumann C. House dust mite-specific T cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. *J Allergy Clin Immunol* 1992;**89**:801–810.
- Di Prisco de Fuenmayor MC, Champion RH. Specific hyposensitization in atopic dermatitis. *Br J Dermatol* 1979;**101**:697–700.
- Ring J. Successful hyposensitization treatment in atopic eczema: results of a trial in monozygotic twins. *Br J Dermatol* 1982;**107**:597–602.
- Zachariae H, Cramers M, Herlin T, Jensen J, Kragballe K, TERNOWITZ T et al. Non-specific immunotherapy and specific hyposensitization in severe atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1985;**114**:48–54.
- Seidenari S, Mosca M, Taglietti M, Manco S, Nume G. Specific hyposensitization in atopic dermatitis. *Dermatologica* 1986;**172**:229.
- Pacor ML, Biasi D, Maleknia T. The efficacy of long-term specific immunotherapy for *Dermatophagoides pteronyssinus* in patients with atopic dermatitis. *Recenti Prog Med* 1994;**85**:273–277.
- Trofimowicz A, Rzepecka E, Hofman J. Clinical effects of specific immunotherapy in children with atopic dermatitis. *Rocz Akad Med Bialymst* 1995;**40**:414–422.
- Galli E, Chini L, Nardi S, Benincori N, Panei P, Fraioli G et al. Use of a specific oral hyposensitization therapy to *Dermatophagoides pteronyssinus* in children with atopic dermatitis. *Allergol Immunopathol* 1994;**22**:18–22.
- Leroy BP, Boden G, Lachapelle JM, Jacquemin MG, Saint-Remy JM. A novel therapy for atopic dermatitis with allergen-antibody complexes: a double-blind, placebo-controlled study. *J Am Acad Dermatol* 1993;**28**:232–239.
- Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. Severity scoring of atopic dermatitis: The SCORAD index. *Dermatology* 1993;**186**:23–31.
- Mastrandrea F. Immunotherapy in atopic dermatitis. *Expert Opin Investig Drugs* 2001;**10**:49–63.
- Werfel T, Morita A, Grewe M, Renz H, Wahn U, Krutmann J et al. Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J Invest Dermatol* 1996;**107**:871–876.
- Grewe M, Bruijnzeel-Koomen CA, Schopf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. *Immunol Today* 1998;**19**:359–361.