

BRIEF REPORT

Sublingual immunotherapy
efficacy in patients with atopic
dermatitis and house dust mites
sensitivity: a prospective pilot
study

Gianni Cadario ^a, Antonia G. Galluccio ^b, Michele Pezza ^b,
Antonella Appino ^a, Massimo Milani ^c Silvia Pecora ^c and
Fulvio Mastrandrea ^d

^a S. Giovanni Battista Hospital, Allergy Clinical Immunology, Turin, Italy

^b Unità Operativa di Dermatologia Venereologia "Sacro Cuore di Gesù"
Fatebenefratelli Hospital, Benevento Italy

^c ALK-Abellò Italy, Medical Department, Lainate, Italy

^d SS Annunziata Hospital, Allergy Clinical Immunology Division, Taranto, Italy

Address for correspondence: Dr Massimo Milani, MD, Medical Director, ALK-Abellò Italy,
Via Ramazzotti 12, Lainate, Milan, Italy. Tel.: +39 0293763356; Fax: +39 0293763450;
e-mail: massimo.milani@it.alk-abello.com

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ABSTRACT

Background: Specific subcutaneous immunotherapy (SCIT) with house dust mite (HDM) preparation has recently been shown to improve eczema in patients with atopic dermatitis (AD). So far, there is less data regarding efficacy and safety of specific sublingual immunotherapy (SLIT) in patients with AD.

Study aim: To evaluate in an open non-controlled, non-randomized pilot trial the effect of SLIT with HDM allergen extracts preparation (SLITone, ALK Abellò Italy) on SCORAD in adult patients with mild–moderate AD.

Patients and methods: 86 Subjects (53 females and 33 males) between 3 and 60 years of age with AD and IgE-proved (Class > 2) HDM sensitization were enrolled after their informed consent in the trial. Exclusion criteria were severe asthma and treatment with systemic or high potent topical corticosteroids or immunosuppressant agents. Patients were treated with SLIT (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts: SLITone, ALK-Abellò) for at least 12 months. SCORAD was evaluated at baseline and after 12 months of treatment.

Results: Baseline SCORAD value, mean ± SD, was 43.3 ± 13.7 (range 15–84). After 1 year of

SLIT, mean ± SD, SCORAD value was reduced to 23.7 ± 13.3 (range: 0–65) (p = 0.0001; unpaired t-test vs. baseline). This was a 46% reduction in SCORAD in comparison with baseline value. A significant improvement, defined as a SCORAD reduction of > 30%, was observed in 51 out of 86 patients (59%). In 5 patients (5.8%) SCORAD values did not change at the end of the observation period. In 30 patients (35%) the SCORAD reduction after SIT was ≤ 30% in comparison with baseline. Total and specific IgE serum levels were significantly (p = 0.001) reduced after SLIT. No severe adverse events were observed during the trial.

Conclusion: In this open non-controlled trial SLIT with HDM extracts in patients with mild to moderate AD was effective in reducing the SCORAD after 1 year of SLIT treatment. In addition the treatment was very well tolerated. Treatment with SLIT, furthermore, has allowed a gradual and relevant reduction of concomitant therapies with topical corticosteroids or immunosuppressants. Present results require further controlled trials in order to confirm the potential clinical benefit of SLIT in this clinical setting.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory itching skin disease that affects a large number of children and adults¹. The onset of AD generally occurs during the first 6 months of life. In adults with AD only 17% had onset after adolescence². AD may arise from dysregulation of IgE and T cell mediated hypersensitivity reactions. Atopy is significantly associated with manifestation and severity of AD, especially in children³. Exposure to aeroallergen (mites and pollen) has been shown to increase the risk factors for AD and AD severity⁴. Children with AD are at a high risk of allergic asthma and allergic rhinitis. Furthermore, aeroallergens are a trigger for exacerbations in adult AD⁵. In about 80% of adult patients with AD, the disease is associated with increased serum IgE levels, sensitisation against aeroallergens and concomitant allergic rhinitis and asthma⁶. To date, specific immunotherapy (SIT) is not an established therapeutic approach for the treatment of AD. Some controlled trials have failed to show clinical efficacy of SIT in the treatment of AD⁷. However, SIT with house dust mite (HDM) subcutaneous preparation has been recently demonstrated, in a randomized double-blind trial, to improve eczema in patients with AD⁸. In comparison with subcutaneous SIT, sublingual immunotherapy (SLIT) is considered a more convenient and safer approach for the treatment of some forms of allergies⁹. So far, there are few and conflicting data regarding the efficacy and safety of Sublingual Immunotherapy (SLIT) in patients with AD.

Study aim

To evaluate efficacy and safety of SLIT with mite allergen extracts in AD patients with house dust mite sensitization on Severity Scoring of Atopic Dermatitis (SCORAD) index.

Study design

We conducted a multi-centre open, non-controlled, non-randomized pilot trial in third-level specialist hospitals (two Allergy Units and one Dermatology Department).

Patients and methods

A total of 86 patients (53 women and 33 men) between 3 and 54 years of age, mean (SD) age: 26 (12), with chronic AD and IgE-proved (Class > 2; i.e. > 3.4 kUa/L) (CAP-FEIA, Pharmacia, Uppsala Sweden) HDM sensitization were enrolled after their informed consent. The study started in November 2004 and was concluded

in January 2007. All patients met the Hanafin and Rajika diagnostic criteria for AD¹⁰. Patients, after their informed consent, were treated with SLIT (Dermatophagoides p. and Dermatophagoides f. mix extracts: SLITone HDM mix, ALK-Abellø, maintenance daily dose: 0.8 and 0.4 µg of Der 1 and Der 2 major allergens, respectively) for at least 12 months, with a 10-day induction phase (build-up phase). The prescribed SLIT was prepared as a glycerinated solution for sublingual administration. The extract was standardized through immunological and bioequivalence methods. Build-up and maintenance doses were expressed in STU (Standardized Treatment Units). The daily maintenance dose was a volume of 0.2 mL of 1000 STU/mL solution. The drug had to be taken in the morning before breakfast. SCORAD index was evaluated at baseline and after 12 months of treatment. The SCORAD index is a tool used to assess the severity of AD by combining evaluation of extent, intensity of lesions and subjective symptoms such as itch and sleep loss¹¹. Total serum IgE levels were measured at baseline and after 12 months of SLIT treatment. Specific IgE serum levels against Der P1 allergen (Pharmacia CAP System RAST) were also measured after SLIT in 53 patients. Patients with allergic bronchial asthma, with a history of immunotherapy in the last 3 years, patients treated with UV or with group IV topical steroid were excluded from the study. Additional exclusion criteria were treatments with systemic corticosteroid or immunosuppressant agents. The primary outcome measure of the study was the mean difference between the average of the SCORAD value at baseline and after 12 months of treatment with SLIT. Secondary end points were percentage of patients with a significant reduction in SCORAD defined as % reduction of scored of 30% or more and the evolution of total and specific serum IgE levels.

Statistical analysis

All statistical analyses were carried out using SPSS version 13 software. For statistical tests we used parametric (for normal distributed variables) and non-parametric (for not normal distributed variables) methods. All tests were two-tailed. The level of significance was $\alpha = 0.05$.

Results

(a) Demographic and baseline data

Table 1 reports the clinical and demographic characteristics of enrolled patients. Baseline SCORAD index value, mean $\pm$ SD, was 43.3 ± 13.7 . SCORAD index values ranged from 15 to 84. AD was mild (i.e. SCORAD < 35)

in 15 patients (17%), moderate in 62 (73%) (SCORAD between 35 and 60) and severe (i.e. SCORAD > 60) in 9 (10%) subjects. Topical treatments utilized at baseline were mainly calcineurin inhibitors and corticosteroids.

(b) SLIT treatment and SCORAD evolution

After 1 year of SLIT treatment the SCORAD value was 23.7 ± 13.3 ($p = 0.0001$; unpaired t -test) (range: 0–65). The absolute difference in SCORAD, in comparison with baseline, was 19.6 (95% CI of difference: from 15.8 to 23.3) (Figure 1). This represented a 46% reduction in SCORAD. A significant improvement, defined as a SCORAD index reduction of > 30%, was observed in 51 out of 86 patients (59%). In 5 patients (5.8%) SCORAD values did not change at the end of observation period. In 30 patients (35%) the SCORAD reduction after SLIT was $\leq 30\%$ in comparison with baseline. After SLIT, 70 out of 86 subjects had a SCORAD < 35. In 60 patients (69%) the SCORAD values at baseline were above 40 (mean $\pm$ SD: 51 ± 9). In these patients the SCORAD decreased to 26 ± 15 (50% reduction) after SLIT treatments.

(c) SLIT treatment and IgE serum levels

Total IgE serum levels, mean $\pm$ SE, were significantly reduced after SLIT, from 294 ± 38 kU/L to 74 ± 4.7 kU/L, at the end of 1 year of SLIT treatment ($p = 0.0001$; Mann–Whitney test). For 53 patients RAST specific IgE values were available both at baseline and after SLIT treatment: a significant ($p = 0.001$, Mann–Whitney Test) reduction after SLIT treatment was observed (from 3.4 kU/L to 1.3 kU/L) (Figure 2). At baseline there was no correlation between SCORAD values and total or specific IgE serum levels. Furthermore we did not find any correlation between SCORAD absolute reduction and total or specific IgE serum levels reduction.

(d) SLIT treatment and concomitant topical drugs

Regarding concomitant topical treatments, at the end of 1 year of SLIT therapy, 52% of patients were treated with emollient creams only, 20% with emollient creams and topical calcineurin inhibitors, 10% with topical corticosteroids and 12% with oral antihistamine compounds only. An additional 6% of patients needed no topical treatments for AD. Therefore, at the end of SLIT treatment we observed a trend in reducing the use of topical corticosteroid and topical calcineurin inhibitor drugs in comparison with baseline (topical corticosteroid: 10% vs. 36%; topical calcineurin inhibitors: 20% vs. 49%). No severe adverse events were observed during the trial.

Table 1. Baseline characteristic of 86 AD patients treated with SLIT

Men, n(%)	33 (40%)
Women, n(%)	53 (60%)
Mean $\pm$ SD age, years	26 ± 12
Mean $\pm$ SD duration of AD, years	22 ± 10
AD severity (% patients) at baseline	
Mild	17%
Moderate	73%
Severe	10%
Total IgE, mean $\pm$ SE, kU/L	294 ± 38
Specific IgE, mean $\pm$ SE, kUa/L	3.2 ± 0.2
Topical treatment for AD (% patients) at baseline	
Emollient cream	22%
Corticosteroid	36%
Calcineurin inhibitors	49%



Figure 1. Evolution of SCORAD index at baseline and after 1 year of SLIT treatment ($n = 86$); $p = 0.0001$ paired t -test

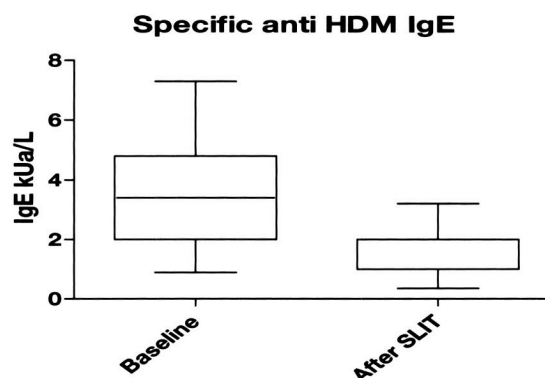


Figure 2. Modification of specific IgE serum levels at baseline and after 1 year of SLIT treatment ($n = 86$); $p = 0.001$ Mann–Whitney test

Discussion

AD is frequently the first clinical manifestation of atopic disease in infancy¹². Basic therapy of AD comprises optimal skin care, emollient creams, topical corticosteroids and/or topical calcineurin inhibitors. Despite a strong rationale, hyposensitization with specific immunotherapy is not an

established strategic treatment of AD¹. However, a recent study has shown that SCIT with HDM allergen extracts in adults AD patients with positive skin test toward HDM allergens is effective in reducing the SCORAD index and reducing, in the mean time, the need for topical corticosteroids⁸. A wide clinical use of SCIT is, however, limited by the inconvenience and safety profile of this route of administration. A sublingual route has emerged as an effective alternative to subcutaneous immunotherapy¹³. A recent trial, performed in children with AD, has shown that SLIT with HDM extracts could be effective in mild and moderate disease¹⁴. In this open non-controlled trial SLIT with HDM extracts in patients with mild-to-severe AD and sensitivity to HDM allergens was effective in reducing the SCORAD index after 1 year of treatment. SLIT has induced also a significant reduction in total and specific IgE levels. In addition SLIT was very well tolerated. This treatment, furthermore, has allowed a gradual and complete withdrawal of concomitant therapies with topical corticosteroids or immunosuppressants. However, some limitations should be taken into account in evaluating the results of the present trial. This was an open non-comparative non-randomized pilot trial. It is known that AD severity could present spontaneous remissions over time. Therefore, the modification of SCORAD index values we observed in these patients could be only partially induced by SLIT. However, the majority of patients enrolled in this trial were mainly adults (mean age 26 years) with a chronic form of AD and who had suffered from AD for several years. The mean absolute reduction of SCORAD index was clinically relevant (-19 points). In the trial conducted by Werfel *et al.*⁸, with a randomized placebo-controlled double-blind design, the control group has shown, after 1 year, a SCORAD index reduction of -7 points. In the active, high-dose SCIT group a -21 points reduction in the SCORAD index was observed at the end of 1 year of treatment. Furthermore, we found a significant reduction both in total and specific IgE serum levels after SLIT. Even if some authors suggest that there is no correlation between clinical evolution of AD and IgE levels modifications¹⁵, our data strongly suggest that SLIT can modulate the immune system in patients with AD and HDM sensitivity.

Conclusion

SLIT with HDM standardized extracts has shown in this open non-randomized pilot trial to have an effect

in reducing the SCORAD index in patients with AD. Further placebo-controlled randomized trials are warranted in order to confirm potential clinical benefit of SLIT in this clinical setting.

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