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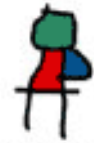
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Allergologia et immunopathologia

INTERNATIONAL JOURNAL FOR CLINICAL AND INVESTIGATIVE ALLERGOLOGY AND CLINICAL IMMUNOLOGY
ORGANO OFICIAL DE LA SOCIEDAD ESPAÑOLA DE INMUNOLOGÍA CLÍNICA Y ALERGIA PEDIÁTRICA



Sociedad Española de Inmunología
Clínica y Alergia Pediátrica
(S.E.I.C.A.P.)

Miércoles 1 Marzo 2000. Volumen 28 - Número 2 p. 54 - 62

Original articles

Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up of 35 consecutive patients

F Mastrandrea G Serio M Minelli A Minardi G Scarcia G Coradduzza

Resumen: la inmunoterapia específica ha demostrado ser efectiva en pacientes con enfermedades respiratorias mediadas por IgE y se están estudiando nuevas rutas de administración alternativas. La Dermatitis atópica (DA) está en la actualidad considerada como una enfermedad alérgica inflamatoria. Métodos: hemos llevado a cabo un estudio de cohorte para evaluar la seguridad y eficacia de la inmunoterapia por vía sublingual (SLIT) en un grupo de pacientes seleccionados que padecían DA extrínseca. Se han incluido 35 pacientes, 16 de ellos con DA sin síntomas respiratorios (grupo A) y 19 con DA asociada a asma leve y/o rinitis (grupo B). La intensidad de las lesiones cutáneas (eczema) se ha graduado en una escala de 0-4, en relación al más reciente Índice SCORAD, donde 0 correspondía a la completa curación del eczema y 4 correspondía a la extensión máxima de las lesiones. Solamente los pacientes con eczema entre 1 y 3 recibieron SLIT durante 36 meses. La graduación del eczema, los síntomas y los efectos adversos se registraron durante visitas de control realizadas cada dos meses durante los dos primeros años y luego a los 36 meses. Después de la interrupción de la SLIT, a todos los pacientes se les hacía un seguimiento anual durante tres años para evaluar los efectos a largo plazo del tratamiento. Todos los pacientes siguieron una serie de normas de conducta con el fin de controlar las variables externas que pudiesen confundir los resultados. Todos los pacientes recibieron ketotifeno durante los tres primeros meses de SLIT. Resultados: para la evaluación de la eficacia, solamente se ha considerado la completa desaparición de las lesiones de piel (score 0). Esta evolución fue

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observada en el grupo A en el 12,6% de los pacientes después de seis meses de tratamiento, en el 31,7 a los 12 meses y en el 68,8% después de 24 meses. En el grupo B, el eczema desapareció en el 0% después de seis meses, en el 36,8% después de 12 meses y en el 73,7% tras 24 meses. Ningún paciente del grupo A desarrolló asma durante el tratamiento, mientras que un paciente padeció asma tres años después de haber cesado la SLIT. Se detectaron tres reacciones locales que consistieron en dos eczemas leves y diarrea. La única reacción sistémica observada fue un caso de urticaria, debido a la violación del esquema de administración. No hubo ninguna reacción que amenazara la vida. Conclusiones: los resultados obtenidos, teniendo en cuenta los límites del diseño del estudio, sugieren que la SLIT en el tratamiento de la forma extrínseca de la DA es segura y bien tolerada por los pacientes y podría alterar favorablemente al curso natural de la enfermedad.

Palabras clave: Dermatitis atópica. Alergenos. Inmunoterapia. Sublingual específica. Efectividad. Seguridad.

Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up of 35 consecutive patients

Background: allergen-specific immunotherapy has proved to be effective in selected patients with IgE-mediated respiratory allergic diseases, and alternative routes of administration are being studied. Atopic Dermatitis (AD) is currently regarded as an allergic inflammatory disease. Methods: we conducted a cohort study to evaluate the safety and effectiveness of sublingual-swallow immunotherapy (SLIT) in selected patients with allergic (extrinsic) AD. Thirty-five patients, 16 suffering from AD without respiratory allergic symptoms (Group A) and 19 with AD associated to mild asthma and/or rhinitis (Group B), were enrolled in the study. The severity of the skin lesions (eczema) was scored on a 0 to 4 scale (and subsequently related to the more recent SCORAD Index), where 0 indicated complete healing of the eczema and 4 indicated maximal spread of the lesions. Only patients with an eczema score of 1 to 3 were started on allergen-specific SLIT for 36 months. Eczema scores, symptoms and side effects were recorded every two months during the first 2 years and then after 36 months. After SLIT was completed, all patients attended 3 yearly follow-up visits to evaluate the long-term effects of the treatment. All patients followed a set of rules designed to control for identified confounding variables. All patients received ketotifen during the first 3 months of SLIT. Results: only the complete disappearance of skin lesions (score 0) was considered to indicate effectiveness. In Group A this was observed in 12.6% of the patients after 6 months of SLIT, in 31.2% after 12 months and 68.8% after 24 months. In Group B, eczema disappeared in 0% after 6 months, in 36.8% after 12 months and 73.7% after 24 months. No patients in Group A developed asthma during SLIT, and 1 patient developed asthma 3 years after immunotherapy had ended. Three focal reactions consisting of 2 cases of mild eczema and one case of diarrhoea were recorded. One case of urticaria, due to violation of the administration schedule was the only systemic reaction observed. No life-threatening reactions appeared at any time of the study. Conclusions: the outcomes obtained, taken into account the limitations of the study design, suggest that sublingual allergen-specific immunotherapy for the treatment of the extrinsic form of Atopic Dermatitis is safe and well tolerated by patients, and may

favourably affect the natural course of the disease.

Keywords: Atopic dermatitis. Allergens. Sublingual specific immunotherapy. Effectiveness. Safety.

Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up of 35 consecutive patients

F. Mastrandrea*, G. Serio, M. Minelli***, A. Minardi*, G. Scarcia*, G. Coradduzza* and S. Parmiani******

*Allergy and Clinical Immunology Operative Unit, A.O. "S.S. Annunziata", Taranto, Italy. **Medical Statistics, Hygiene Institute, University of Bari, Bari, Italy.

Health Office of Lecce, Lecce, Italy. *ALK-Abellò S.p.A., Lainate, Milan, Italy.

Correspondence:
Silvano Parmiani
ALK-ABELLO" S.p.A.
Via Settembrini, 60
20020 Lainate (Milan) Italy
E-mail: silvano_parmiani@allergia.it

SUMMARY

Background: allergen-specific immunotherapy has proved to be effective in selected patients with IgE-mediated respiratory allergic diseases, and alternative routes of administration are being studied. Atopic Dermatitis (AD) is currently regarded as an allergic inflammatory disease.

Methods: we conducted a cohort study to evaluate the safety and effectiveness of sublingual-swallow immunotherapy (SLIT) in selected patients with allergic (extrinsic) AD. Thirty-five patients, 16 suffering from AD without respiratory allergic symptoms (Group A) and 19 with AD associated to mild asthma and/or rhinitis (Group B), were enrolled in the study. The severity of the skin lesions (eczema) was scored on a 0 to 4 scale (and subsequently related to the more recent SCORAD Index), where 0 indicated complete healing of the eczema and 4 indicated maximal spread of the lesions. Only patients with an eczema score of 1 to 3 were started on allergen-specific SLIT for 36 months. Eczema scores, symptoms and side effects were recorded every two months during the first 2 years and then after 36 months. After SLIT was completed, all patients attended 3 yearly follow-up visits to evaluate the long-term effects of the treatment. All patients followed a set of rules designed to control for identified confounding variables. All patients received ketotifen during the first 3 months of SLIT.

Results: only the complete disappearance of skin lesions (score 0) was considered to indicate effectiveness. In Group A this was observed in 12.6% of the patients after 6

months of SLIT, in 31,2% after 12 months and 68.8% after 24 months. In Group B, eczema disappeared in 0% after 6 months, in 36.8% after 12 months and 73.7% after 24 months. No patients in Group A developed asthma during SLIT, and 1 patient developed asthma 3 years after immunotherapy had ended. Three focal reactions consisting of 2 cases of mild eczema and one case of diarrhoea were recorded. One case of urticaria, due to violation of the administration schedule was the only systemic reaction observed. No life-threatening reactions appeared at any time of the study.

Conclusions: the outcomes obtained, taken into account the limitations of the study design, suggest that sublingual allergen-specific immunotherapy for the treatment of the extrinsic form of Atopic Dermatitis is safe and well tolerated by patients, and may favourably affect the natural course of the disease.

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RESUMEN

Resumen: la inmunoterapia específica ha demostrado ser efectiva en pacientes con enfermedades respiratorias mediadas por IgE y se están estudiando nuevas rutas de administración alternativas. La Dermatitis atópica (DA) está en la actualidad considerada como una enfermedad alérgica inflamatoria.

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La graduación del eczema, los síntomas y los efectos adversos se registraron durante visitas de control realizadas cada dos meses durante los dos primeros años y luego a los 36 meses. Después de la interrupción de la SLIT, a todos los pacientes se les hacía un seguimiento anual durante tres años para evaluar los efectos a largo plazo del tratamiento. Todos los pacientes siguieron una serie de normas de conducta con el fin de controlar las variables externas que pudiesen confundir los resultados. Todos los pacientes recibieron ketotifeno durante los tres primeros meses de SLIT.

Resultados: para la evaluación de la eficacia, solamente se ha considerado la completa desaparición de las lesiones de piel (score 0). Esta evolución fue observada en el grupo A en el 12,6% de los pacientes después de seis meses de tratamiento, en el 31,7 a los 12 meses y en el 68,8% después de 24 meses. En el grupo B, el eczema desapareció en el 0% después de seis meses, en el 36,8% después de 12 meses y en el 73,7% tras 24 meses. Ningún paciente del grupo A desarrolló asma durante el tratamiento, mientras que un paciente padeció asma tres años después de haber cesado la SLIT. Se detectaron tres reacciones locales que consistieron en dos eczemas

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Conclusiones: los resultados obtenidos, teniendo en cuenta los límites del diseño del estudio, sugieren que la SLIT en el tratamiento de la forma extrínseca de la DA es segura y bien tolerada por los pacientes y podría alterar favorablemente al curso natural de la enfermedad.

Palabras clave: Dermatitis atópica. Alergenos. Inmunoterapia. Sublingual específica. Efectividad. Seguridad.

INTRODUCTION

Atopic Dermatitis (AD) is a persistent inflammatory disease involving the skin and very often other organs and systems, mainly the respiratory system (1, 2). The prevalence of AD in infancy is between 10 and 15%, according to available epidemiological studies (3) and about 80% of these subjects have also allergic rhinitis or allergic asthma (2).

Among allergic diseases, AD can be associated to extreme immunological abnormalities (4), specially linked to defects of the lymphocyte system (5). The lack of a widely recognised model of pathogenesis (6) has led to treatments which are mainly symptomatic. Therapies that aim to counteract the immunologic defect have been attempted, and the synthetic thymic hormone thymopentin (7) and IFN-gamma (8) have been shown able to significantly reduce both the severity of the disease and the number of circulating eosinophils. Similar effects have also been shown for cyclosporin (9) and tacrolimus (10).

Although the clinical history as well as the serologic and histopathologic findings strongly suggests an allergic origin for AD, few studies have evaluated the effects of Specific Immunotherapy (SIT) on AD. Only two short-term studies of subcutaneous immunotherapy in patients suffering from AD (12, 13) were reported in the 1998 WHO Position Paper (11). In the first, a double-blind, placebo-controlled trial was conducted for 8 months, and was then followed by a further 6-month treatment period according to a cross-over design. At the end of the study only a trend towards significant reduction in the symptoms could be found (12).

Here we report the results of a 36-month study of sublingual-swallow immunotherapy (SLIT) in 35 consecutive patients with extrinsic AD.

MATERIALS AND METHODS

Study design

This is a retrospective study, based on the analysis of 35 consecutive cases that fulfilled the criteria indicated below.

Patients

Patients were considered eligible if they had positive skin tests to at least one inhalant allergen (score 2-4) and a positive diagnosis for AD (score at least 1).

Patients were excluded from specific immunotherapy when any of the following was present: severe AD (score 4); severe asthma (FEV1 < 70% of the theoretical value); relevant immunologic disorders (unbalanced lymphocytes subpopulations, abnormal serum levels of IgG, IgA or IgM); non-compliance with therapy; other standard contraindications for immunotherapy.

For this retrospective analysis we selected 35 patients with extrinsic AD, diagnosed between 1991-1994. Sixteen of the patients were free from respiratory symptoms (Group A), while 19 had also respiratory allergic symptoms (Group B). After diagnosis, all patients were treated with SLIT for 36 months.

Diagnosis of AD

Patients were diagnosed according to Hanifin and Rajka's criteria (14); variations in the illness during different seasons (perennial, seasonal, mixed Spring-Autumn seasonality) were also taken into account.

Severity of AD was scored during the first visit on a scale ranging from 0 (no skin lesions) to 4 (maximum degree of severity). The SCORAD Index (15) for the evaluation of the severity of AD was not available at that time, but a correlation between our system and the SCORAD Index is shown in table I.

Table I Scoring system for the severity of skin lesions (compared to the current SCORAD system)

-
- 0.Skin completely free from eczema lesions.
 - 1.Lesions covering less than 25% of the body area. Low-grade lesions (SCORAD, B: 1-6). Persistence less than 2 months a year.
 - 2.Lesions covering less than 25% of the body area. Low-grade lesions (SCORAD, B: 1-6) and persistence between 3 and 6 months a year or moderate-grade lesions (SCORAD, B: 6-12) and persistence of lesions less than 3 months a year.
 - 3.Lesions covering between 25% and 50% of the body area. Moderate-to severe-grade lesions (SCORAD, B: 12-18) and persistence for more than 6 months a year.
 - 4.Lesions covering more than 50% of the body area with trend toward generalisation. Severe-grade lesions (SCORAD, B: 12-18) and persistence for more than 6 months a year, with a tendency to persist year-round.
-

Diagnosis of allergy

Allergy to respiratory allergens was diagnosed by skin prick tests with commercial

standardised extracts. Because the skin prick test for food is less reliable, the diagnosis in patients suspected of having food allergy was done *in-vitro* with serum IgE determination, and the effect of IgE-positive food was checked by the standard elimination/ reintroduction procedure.

The clinical history of each patient was also carefully evaluated.

Skin tests

Skin prick tests were done with extracts of Grasses, *Parietaria judaica*, Olive, Mugwort, *Dermatophagoides pteronyssinus* and *D. farinae* standardised in Biological Units with a known content of the major allergen (ALK-Abellò, Milan, Italy) (16). Extracts of *Cupressus spp.*, *Plantago lanceolata* and *Alternaria spp.* standardised in P. N.U (Bayropharm DHS, Milan, Italy) were also used. The skin test response was examined after 15 and 30 minutes and expressed according to a scale of 0 to 4, where 0 indicated a wheal similar to the wheal elicited by the negative control, and 3 a wheal similar to that elicited by 0.1% histamine.

Serum IgE to food allergens

The serum concentration of allergen-specific IgE to milk, egg, casein, soy, peanuts, fish and wheat was determined by the standard RAST method (Pharmacia, Uppsala, Sweden).

Lymphocytes characterisation and quantitative determination of IgG, IgA and IgM in sera

The main lymphocytes subpopulations were evaluated by flow-cytometry (FACScan, Becton-Dickinson, Milan, Italy) with the aid of commercially available monoclonal antibodies specific for CD3, CD4, CD8, CD19, CD23, HLA-DR and CD1a (Becton-Dickinson, Milan, Italy). Serum concentrations of IgG, IgA, IgM were determined by a standard turbidimetric technique (Cobas-Mira, Roche Diagn. System, Roche S.p.A., Milan, Italy).

Identification of the external confounding variables and measures to reduce their effects

Environmental (17-22), dietary (23, 24) and infectious (25-28) factors are able to induce a relapse of inflammation. They are thus able to modify the evolution of AD independently of treatment and the serum IgE level (6, 29), because of their extra-antigenic properties. We therefore developed general rules to be followed by all patients (whether specific IgE-positive or -negative) and special rules to be followed only by IgE positive patients.

General rules (to be strictly followed by all subjects only during the first year of SLIT treatment)

Environmental measures against mites

After diagnosis, all patients were instructed to take standard environmental measures against mites, i.e. frequent vacuuming, washing sheets with hot water ($> 55^{\circ}\text{C}$) at least once a week, removal of plants and soft toys from the patient's bedroom, no use of humidifiers.

Diet

All patients were instructed to avoid eating the following lectin-rich foods: peanuts, nuts in general, crustaceans and shellfish, soy, kiwi and snails. Chocolate and foods or beverages containing food additives (preservatives, dyes, rheologic aids, etc.) were also forbidden.

Only limited quantities were allowed of foods such as tomato, liver, mushrooms, egg white, fermented cheese, spinach and legumes, known to be rich of vasoactive amines or histamine-releasing products.

Personal hygiene

To avoid infection of the eczematous lesions by bacteria and mycetes, careful cleansing of the cutis with mild detergents was recommended. The use of local boric acid solution (2%) was encouraged, while topical drugs based on antibiotics could be used in case of infections.

Other general rules

To avoid any other complication from skin irritation or contact allergy, all patients were instructed to avoid using cosmetics, perfumes and strong detergents. The self-prescription of drugs was forbidden but paracetamol and macrolids were allowed.

Special rules for patients with food allergies

For IgE-positive patients (confirmed by the elimination-reintroduction test) specific rules were developed on an individual basis, according to specific sensitization(s). The offending food was eliminated from the diet when necessary.

Because high-affinity IgE receptors can trigger a type I reaction even with very low amounts of allergen, these rules had to be followed carefully, and the possibility of unidentified additives or components in unsuspected foods also had to be taken into account.

Therapies

Sublingual-swallow immunotherapy (SLIT)

All selected patients with extrinsic AD with or without respiratory symptoms were encouraged to receive SLIT treatment and given complete information. They were also informed that this was an experimental approach supported by our own and published (30) positive outcomes for respiratory and cutaneous symptoms in allergic patients with both problems. All patients accepted the suggested protocol, and gave

their consent in the presence of at least one witness.

SLIT treatments were prepared on an individual basis, selecting clinically relevant allergens from among the skin tests-positive ones according to the standard procedure for respiratory allergies.

Allergens belonging to different families were administered as separate preparations, but not more than two treatments were used in patients sensitized to more than one allergen family. The most common combinations were mites and grasses, mites and *Parietaria*, and grasses and *Parietaria*. *Alternaria* was never used for SLIT.

The therapies consisted of five 5-mL vials (Neo Abellò, Milan, Italy) of allergenic solution in glycerol-saline solution preserved with 0.4% phenol. The major allergen content in one drop of the most concentrated solution used during the maintenance therapy is shown in table II (16).

Table II Major allergen content of the SLIT

Allergen	Major allergen	µg major allergen/ drop of treatment
<i>Dermatophagoides pteronyssinus</i>	Der p 1	0.16
	Der p 2	0.08
<i>Dermatophagoides farinae</i>	Der f 1	0.16
	Der f 2	0.08
Grasses	Group 5	0.1
<i>Parietaria judaica</i>	Par j 1	0.024
<i>Olea europaea</i>	Ole e 1	0.6

The maintenance dose (5 drops of the highest concentration) was reached after 4 weeks of induction with daily administrations of increasing amounts of allergen, and was administered 3 times a week for 3 years. During the pollen season the maintenance dose for pollen allergens was reduced by 60%. Patients were instructed to keep the extract in the mouth for at least 3 minutes after administration, and then to swallow it (combined sublingual-swallow therapy). Treatment with SLIT lasted for 36 months.

Drugs

The administration of SLIT was combined with standard pharmacological treatment for AD. The antihistamine drug Ketotifen was taken according to the standard schedule for this drug during the first 3 months of SLIT. Other drugs (local steroids, oral steroids and oral macrolid antibiotics, the latter two only for the most severe cases) were also prescribed during the first 3 months of SLIT, but only until the skin lesions disappeared.

After this period drugs could be taken only if the eczema worsened, and only after medical examination and prescription. The SLIT schedule was also adjusted if

necessary.

In patients who had also respiratory symptoms, the standard drugs for rhinitis and asthma were prescribed (local beclomethasone dipropionate, salbutamol).

Assessment

During the 3-year period of SLIT, patients were examined regularly every 2 months during the first 24 months, and at 36 months or as necessary, for example if the symptoms worsened. After SLIT was completed, patients were examined regularly at least once a year for 3 more years. A specially designed questionnaire was used to obtain information on any variations in the symptoms and signs of the ongoing skin and respiratory disease, on drug consumption (intake of the prescribed medications was checked, and the use of other drugs was recorded), and on local and/or systemic side effects related to SLIT.

A report based on these periodic observations, including tolerance and efficacy, was prepared for each patient every 6 months during the first year of treatment and then every 12 months for a total of 6 years.

RESULTS

Demographic data

Of all consecutive patients with a diagnosis of extrinsic AD examined in the years 1991-1994, 35 fulfilled the inclusion-exclusion criteria detailed above. Demographic data on patients in Group A (16 patients with AD but without respiratory allergic symptoms) and Group B (19 patients with both AD and respiratory allergic symptoms) are shown in tables III and IV.

Table III Group A Eczema without respiratory allergy (situation on enrolment)

Patient	Age	Sex	Severity score	Allergen sensitisation
1	3	F	3	Grass, Olea, Dp, Df
2	4	M	2	Dp, Df
3	6	F	3	Dp, Df
4	7	M	3	Dp, Df
5	30	M	1	Grass, Olea, Dp, Df
6	7	F	1	Olea, Dp, Df
7	5	M	2	Grass, Olea, Dp, Df
8	13	F	3	Olea, Dp, Df
9	4	M	3	Dp, Df
10*	13	M	2	Grass, Dp, Df
11	6	M	3	Dp, Df
12	7	F	3	Grass, Olea, Dp, Df
13	17	M	3	Dp, Df, Alternaria

14	5	F	3	Dp, Df
15	12	M	3	Grass, Olea, Dp, Df
16*	6	F	3	Parietaria, Dp, Df

*Adverse reactions: relapse of mild eczema, cleared with dose reductions (Dp = *dermatophagoides pteronyssinus*; Df = *dermatophagoides farinae*).

Table IV Group B Eczema associated to mild asthma and/or rhinitis (situation on enrolment)

Patient	Age	Sex	Severity score	Allergen sensitisation
17*	3	F	3	Grass, Olea, Dp, Df
18	7	F	3	Grass, Parietaria
19	18	F	3	Grass, Dp, Df
20	27	F	2	Dp, Df
21**	5	M	2	Dp, Df
22	25	F	1	Grass, Dp, Df
23	28	F	3	Parietaria, Dp, Df
24	3	M	3	Olea, Dp, Df
25	7	F	1	Grass, Olea, Dp, Df
26	18	F	3	Olea, Dp, Df
27	23	F	1	Grass, Olea, Dp, Df
28	8	M	2	Dp, Df
29	9	M	3	Dp, Df
30	5	F	2	Dp, Df
31	23	F	2	Dp, Df
32	22	M	3	Dp, Df
33	23	F	3	Parietaria, Dp, Df
34	12	M	3	Olea, Dp, Df
35	6	F	1	Grass, Parietaria, Dp, Df

Adverse reactions: *diarrhoea during induction, disappeared after slowing the rate of dosage increase; **mild urticaria (see text). (Dp = *dermatophagoides pteronyssinus*; Df = *dermatophagoides farinae*).

Side-effects and tolerability of SLIT

Tolerance of SLIT was excellent. Two patients in Group A reported a reappearance of the eczema after the highest scheduled dose (5 drops from the most concentrated vial). After reduction of the dose to 2 drops of the same vial, the skin lesions disappeared and no other problems were reported during the remainder of the treatment period. One patient in Group A reported diarrhoea during the induction phase; the problem disappeared after treatment was interrupted. Treatment was begun again with a slower schedule (dose increase every 3 days instead of daily) and was very well tolerated with no side effects.

In one 4-year old child a systemic reaction (mild urticaria) was reported, after interruption for 2 months followed by the administration of the highest dose that had previously been well tolerated (5 drops from the most concentrated vial). This side effect was promptly controlled with an oral steroid (betamethasone) and antihistamines.

Efficacy

The disappearance of the skin lesions after 6, 12 and 24 months was taken as the only criterion for efficacy. The prevalence of patients in both groups showing a complete healing of the skin lesions at each observation time is given in table V.

Table V Patients showing a scoring reduction to 0 (eczema clearing) after 6, 12, 24 months of SLIT treatment (%)

	6 months	12 months	24 months
Group A	12.6	31.2	68.8
Group B	0	36.8	73.7

During the follow-up period, only one patient in Group A developed severe asthma but not eczema three years after the interruption of immunotherapy. This subject, polysensitised at enrolment, showed only sensitisation to mites when checked again after the development of asthma. No patient in Group A developed respiratory symptoms and no patients in Group B showed skin lesions within three years after the interruption of immunotherapy.

DISCUSSION

Our study was planned as a retrospective study based on consecutive patients with extrinsic AD who fulfilled predefined selection criteria and who were treated with SLIT. This is an accepted way to study treatment outcomes in diseases such as AD, in which spontaneous variations in time and with age make prolonged treatment and follow-up necessary (31). In our opinion, a double blind, placebo-controlled design, while methodologically appropriate, is neither ethically nor feasible for this kind of disease.

We took steps to minimise the possible effect of known confounding factors that can activate AD by advising patients to follow some simple environmental, dietary and personal hygiene rules.

SLIT was well tolerated throughout the 3-year treatment period. Only two grade 2 and one grade 3 systemic reactions (32) were reported. The systemic reaction occurred after a violation of the administration schedule, and this suggests a more careful evaluation of patient's (or parents') educational level before prescribing self-administered therapy. No life-threatening systemic reactions were recorded at any time during the observation period, confirming that SLIT for AD is as safe and well

tolerated as when this treatment is used for allergic rhinitis and asthma (33-41).

In a recent editorial on SLIT (42), Malling noted that the only parameters of efficacy are a reduction in symptoms and/or a reduction in medication. The magnitude of clinical improvement was also judged very important.

On the basis of these views, we used only the greatest possible magnitude of improvement (complete healing of the eczema, score 0) as the criterion to consider SLIT effective in AD. We should note, however, that at least some improvement with the combined approach we used was seen even in patients whose eczema did not heal completely.

In an open study such as that reported here, the lack of controls, the influence of placebo effect on the final outcome, the effect of spontaneous variations of the disease in time, and the residual effect of pharmacological therapy administered during the first 3 months, must be considered and discussed.

The improvements observed after 6 months in Group A (12.6% patients without eczema) may have been influenced by any of these effects, but the difference in comparison to Group B (0% of the patients free of eczema) raises the question why these factors apparently had no influence in this latter group. A prolonged period of treatment is able to compensate for the possible effects of these confounding factors, and we observed significant clinical improvement after 12 and especially after 24 months.

Another important point when considering the use of specific immunotherapy to treat AD is its capacity to modify the immune response. This property makes it possible to influence the natural history of the disease, as was shown for respiratory allergic diseases (11, 32).

As mentioned in the introduction, Leung (2) reported that up to 80% of the subjects with AD could develop allergic rhinitis or asthma later in childhood, and that eczema often clears as respiratory allergy develops. This common progression, known as "the allergic march from Atopic dermatitis to allergic asthma", has been extensively investigated mainly in the paediatric population. Bergmann and co-workers (43) found that 40% of infants with Atopic dermatitis in early infancy are likely to develop asthma at the age of 4 years. In a well designed 1-year study to evaluate the prophylactic effect of ketotifen in preventing the onset of asthma (44), other authors reported that 25 children (41.6%) in the placebo group developed asthma, whereas only 8 children (13.1%) in the ketotifen-treated group did. In our study no patient (0%) in Group A developed asthma during the first year of SLIT or at any other time throughout the treatment period. All patients included in the study were treated with ketotifen during the first three months of the study. Even if we accept a prolonged influence of a residual pharmacological effect, comparison with the rate of appearance of asthma in the group that received active treatment (45) suggests that specific immunotherapy is capable of influencing the natural history of the disease.

In subjects from both groups in whom the skin lesions healed completely after 24 months of SLIT (68.8% in Group A and 73.8% in Group B) no relapses of eczema occurred during the subsequent 3 years without therapy. Furthermore, patient n.1

from Group A showed sensitivity to many allergens before starting immunotherapy, but only to mites when asthma developed 3 years after SLIT was completed.

These observations are in keeping with the results of several trials reporting the long-term effect of injective immunotherapy (46-49) in respiratory allergy, and an influence on the allergen sensitisation (50).

Sublingual-swallow immunotherapy appears to be an effective treatment for AD, with an excellent safety and compliance profile; it also represents a promising model to increase our understanding of the mechanism of action of allergen specific immunotherapy. It has been suggested that specific immunotherapy is able to induce immune deviation of TH2 and TH0 T-cell responses in favour of TH1 responses (51, 52), to reduce TH2 responses (53) or to induce anergy (54, 55). Circulating allergen-specific TH2 cells are currently believed to home on the target organ tissue (56), where they contribute to allergic inflammation. According to this model, any immunological effect on such cells involves a long-distance delivery of the therapeutic allergenic extract from the site of administration to the peripheral, tissue-infiltrating, TH2 cells. The resulting extremely low dilutions of allergen have raised the frequently debated issue of the amount of allergen extract to be administered (41, 42).

Bagnasco and co-workers, in an elegant experiment with a radiolabelled allergen (57), proved that in the oral mucosa the allergen was not absorbed but persisted for prolonged periods. These findings suggest that the oral mucosa immune system is involved in the effects of treatment.

We recently suggested another hypothesis compatible with the proven local response, the very low allergen concentration and the observed systemic effect of SLIT (58). According to our hypothesis, the locally administered allergen may induce an over-expression of the vascular adhesion molecules in the vessels of the oral mucosa. This proposed mechanism resembles the mechanism of action of the "Atopy patch test", that recruits allergen-specific mononuclear cells *in-situ* very rapidly because of the high allergen concentration. The inflammatory cells are recruited (albeit in low numbers) at the site of administration, where they remain throughout treatment and are subjected to the local immunological actions of the antigens/ allergens. Our hypothesis accounts for the well-documented contribution of the bone marrow to the delivery of hemopoietic precursors to the peripheral sites of allergic inflammation (59, 60). The identification of CD34+ hemopoietic precursors, and the presence of different cell phenotypes characteristic of early developmental stages of myeloid and lymphoid cell lineages (61, 63) suggest that the immunological actions of the therapeutical extract may be targeted not only to mature cells (i.e. CD4+ TH2) but also to immature cells. In the light of the current body of evidence, immunotherapy may work by inducing persistent suppression of the established antigen-specific TH2 cells (64), and by interfering with TH2 clones generation (6) through a negative selection mechanism.

Regardless of the mechanism involved, we have shown that SLIT is able to provide clear clinical benefits to patients with extrinsic AD, both during therapy and for up to at least 3 years after treatment is completed.

In conclusion, although the limitations of the study design do not permit

generalisations, we support the use of SLIT to treat low and moderately severe forms of extrinsic AD because of its safety, good tolerance and capacity to influence the course of AD. Confounding variables should be carefully identified and controlled for to achieve the best results.

We hope that our proposal will serve as the starting point for more exhaustive studies designed to determine the role of SLIT in extrinsic AD.

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