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Original Article

Sublingual immunotherapy with a *Dermatophagoides pteronyssinus* extract in mass units: assessment of efficacy, safety and degree of compliance

Background: Sublingual immunotherapy (SLIT) with allergenic extracts is being increasingly used in clinical practice, and its efficacy and safety have been documented in a number of studies. The aim of this study was to assess these two parameters in two groups of patients (children and adults) with sensitization to a perennial allergen (*Dermatophagoides pteronyssinus*), and also to establish the degree of compliance with the treatment. **Methods:** A symptoms and medication score was recorded at the beginning and at the end of a one-year treatment course with SLIT. The degree of compliance was assessed by means of the correlation between protocol compliance and a questionnaire containing a critical opinion of the patient regarding SLIT. **Results:** Most patients (84%) felt better or much better at the end of one year of treatment. Statistically significant differences were observed in the nasal, ocular and total symptoms scores, as well as in the joint symptoms and medication one. The percentage of systemic reactions was 0.3. The degree of protocol compliance was good or very good in 72% of the cases, and these patients evidenced a statistically significant correlation between this parameter and a positive opinion towards SLIT. **Conclusion:** SLIT is an effective and well-tolerated therapeutic modality, and the patients show a high degree of compliance.

Key words: Compliance. *Dermatophagoides pteronyssinus*. Efficacy. Safety. Sublingual immunotherapy.

Inmunoterapia sublingual con un extracto de *Dermatophagoides pteronyssinus* valorado en unidades de masa: evaluación del grado de cumplimiento, seguridad y mejoría clínica

Fundamento: El uso de vacunas alérgicas administradas por vía sublingual (sublingual immunotherapy, SLIT) es cada vez mayor, y son numerosos los estudios en que se demuestran su eficacia y su seguridad. El objetivo del presente estudio era establecer, en dos grupos de pacientes (niños y adultos) con enfermedad alérgica respiratoria por sensibilización a *Dermatophagoides pteronyssinus*, además de los dos parámetros anteriores, el grado de cumplimiento de los pacientes hacia el tratamiento. **Métodos:** Se analizó la evolución clínica de los pacientes tras un año de tratamiento, mediante puntuación de síntomas y medicación. El grado de cumplimiento se valoró correlacionando el cumplimiento

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del estudio con un cuestionario que contenía un juicio crítico del paciente respecto a la SLIT. **Resultados:** El 84% de los pacientes se encontró mejor o mucho mejor al finalizar el año de tratamiento; se encontraron diferencias estadísticamente significativas en los síntomas nasales, oculares, síntomas totales y puntuación del conjunto de síntomas y medicación. El porcentaje de reacciones sistémicas por dosis fue de 0,3. El grado de cumplimiento del protocolo fue bueno o muy bueno en el 72% de los pacientes; en estos pacientes la correlación entre este parámetro y la existencia de un juicio crítico positivo fue significativa. **Conclusión:** Los extractos alérgicos administrados por vía sublingual han demostrado ser un tratamiento seguro y eficaz. Se ha objetivado en los pacientes un alto grado de cumplimiento hacia esta forma de inmunoterapia.

Palabras clave: Cumplimiento. *Dermatophagoides pteronyssinus*. Eficacia. Inmunoterapia sublingual. Seguridad.

In a number of double-blind, placebo-controlled studies¹⁻⁶, sublingually-administered allergenic extracts have been demonstrated to be an effective therapeutic modality in respiratory allergic disease. Their level of tolerance has also been confirmed in pharmacovigilance studies both in adults⁷ and in children⁸. Furthermore, and according to the publications of the EAA-CI and ESPACI Immunotherapy Committees⁹, among all the alternatives that have been investigated to the subcutaneous administration of allergenic hyposensitising therapy with the purpose of increasing the safety and comfort of administration to the allergic patient, the sublingual route has been shown to be the clinically most effective one^{4,10}.

Even though these data are fundamental at the time of selecting a given therapeutic modality, the attitude of the personnel involved in the administration and follow-up of the treatment and the degree of cooperation of the patient himself are fully as important in the quest for therapeutic success. There is at present so little information regarding the latter aspect that we have decided to assess, using the tools usually available in the everyday clinical practice of Allergology and in two groups of patients (children and adults), not only the safety and efficacy of this therapy after one year of follow-up but also the degree of compliance of the patients with sublingually-administered allergenic extracts.

Table I. Items considered in the patients' critical assessment

A/ Treatment

1. The administration was easy and comfortable.
2. Had difficulties in remembering the schedule.
3. It was easy to follow the instructions for administration.
4. Discomfort or adverse side effects occurred.
5. If the answer to (4) was affirmative, did you consider those effects important?
6. Forgot to take the treatment on occasion.
7. If the answer to (6) was affirmative, was it easy to re-start the schedule?
8. Understood the physician's instructions well.
9. Understood the nurse's/technician's instructions well.

B/ Symptom and Medication Control Cards

10. Understood the instructions for completing the card well.
11. Found the card easy to complete.
12. Found completing the card to be unnecessary/bothersome.

C/ Sublingual Immunotherapy Control Cards

13. Found completing them useful as a means to remember the therapy schedule.
14. Found completing them useful as a means to remember the adverse side effects that occurred.
15. Found it too long to complete these cards over one year.

MATERIAL AND METHODS

Study population: Sixty-three patients were entered into the study, 30 children aged between 6 and 14 years and 33 adults aged 18 to 50 years. All of them had a diagnosis of allergic rhinitis and/or mild asthma due to *Dermatophagoides pteronyssinus* sensitization. The diagnosis was established through the clinical history supported by (a) skin tests (prick test, *D. pteronyssinus* extract, 100 BU/ml, ALK-Abelló, Madrid, Spain), in which any wheal greater than 3 mm² in area was considered positive, and with 10 mg/ml-histamine and normal saline as positive and negative controls, respectively, and (b) IgE quantitation (CAP Pharmacia, Class ≥ 2).

All the patients received, further to the corresponding drug therapy, sublingual immunotherapy (SLIT® Tratamiento Sublingual, *D. pteronyssinus* 100%, ALK-Abelló). Each patient was reviewed, including the recruitment visit, seven times in the course of the study period.

Clinical improvement: This was assessed through the degree of symptom control and use of medication for a period of four weeks prior to the beginning of immuno-

Table II. Characteristics of the study patients

	Gender (%)		Age (years)				Diagnosis (%)		
	Males	Females	N	m	SD	SEM	RC	A	RC + A
Adults	49	41	33	24.6	7.6	1.3	50	33.3	16.7
Children	63	37	30	8.8	2.3	0.4	76	0	24
Overall	56	44	63	17.1	9.8	1.2	63	16	21

N = Number of patients; m = arithmetic mean; SD = standard deviation; RC = rhinoconjunctivitis; A = asthma.

therapy, in October-November 1997, and for a similar period in 1998, during the administration of SLIT. Each patient was given a diary card in which he/she noted both the intensity of symptoms and the use of medication. According to intensity, the symptoms were scored between 0 and 3. The physician's assessment of the patient's clinical situation was also considered.

Safety: Each patient received a diary card for control of the immunotherapy administration, with instructions to note down the immunotherapy doses, dates of administration and any incidences or symptoms both immediate and late. The card was then assessed by the physician, who noted the adverse reactions in the Data Collection Booklet. The severity of the reactions was classified according to the European Academy criteria¹¹. Itching of the tongue, lips and/or mouth and ocular pruritus were classed as local reactions.

Compliance: The assessment was based firstly on the degree of protocol compliance (considering whether the patients attended the review visits on the scheduled dates and assessing the completion of the diary cards, both the ones for treatment administration follow-up - SLIT Follow-Up Cards-, in which the patient was to consign all the doses administered and any adverse reaction occurring, and those used for the assessment of symptoms and medication, which were to be completed over a period of four weeks in October - November), and secondly

on the answers to a 15-item questionnaire in which the patient gave his critical opinion about the SLIT treatment (Table I) after the end of the one-year follow-up period. Finally, the degree of correlation between the two parameters was established.

Statistical and data processing methodology: In the case of the qualitative variables, the absolute frequency and the relative frequency (or percentage) were calculated. For the quantitative ones the calculated values were the mean, the standard deviation and the standard error. When a variable had a bad fit to a Gaussian distribution, the median and interquartile track were calculated. The fit to a normal distribution was assessed through the Shapiro-Wilk test. For comparisons of the means for paired data the Wilcoxon test was used. In the assessment of scalar data both the absolute and the relative (to the baseline value) scores were considered. The Spearman and Kendall correlation coefficients were used for the analysis of compliance, as the variables were non-parametric.

The SAS® System was used both for the generation of the database and for the analyses of the data (the BASE and FSP modules for information management tasks and the STAT and GRAPH ones for acquisition and analysis of the results). For the data management a double-introduction system was used with later assessment and correction of mistakes.

Table III. Systemic adverse reactions: description

Reaction	Time of occurrence			Treatment		Age of the patient	
	No	Immediate	Late	Yes	No	Adults	Children
Epigastralgia	1		1		1	1	
Rhinitis	11	5	6		11	5	6
Cough	2		2		2		2
Headache	1		1		1		1
Dyspnoea	1		1	1		1	

Table IV. Percentages of adverse reactions, per dose and age group

Adults			Children			Overall		
RL	RS	RT	RL	RS	RT	RL	RS	RT
0.06	0.32	0.38	0.07	0.33	0.4	0.04	0.3	0.35

RL = local reactions; RS = systemic reactions; RT = total reactions.

RESULTS

Sample description: The main characteristics of the patient population are summarised in Table II. The duration of the allergic disease had been greater for the adults than for the children (5.2 ± 5.6 and 3.4 ± 1.2 years, respectively). The total number of patients dropping out was 6 (3 adults and 3 children); in all cases save one, the dropout was due to causes not related to the therapy given (the one exception was a case of mild yet repeated adverse reactions). Ten adults and one child abandoned the study population before the beginning of the immunotherapy administration, after having been included into the study population.

Doses administered: The therapy schedule used was the one recommended by the manufacturer, which starts with one drop from Vial 0 and increases gradually to the maximum dose (5 drops from Vial 4); this maximum dose is then repeated thrice weekly in the maintenance phase. The total number of doses administered was 4,954 (2,708 to children and 2,246 to adults); 31% of the doses corresponded to the dose increase phase. All the patients who continued therapy into the maintenance phase had reached the maximum dose foreseen in the protocol, 5 drops (equivalent to 2 BU, 0.8 µg Der p 1) from the highest-concentration Vial 4 (1,000 STU/ml, equivalent to 10 BU/ml).

The mean number of doses administered was 95.3 ± 15.8 (93.4 ± 18.0 in children and 97.7 ± 15.8 in adults). The cumulative dose after completion of the one-year treatment period was 224.6 BU (equivalent to 89.8 µg Der p 1). The corresponding group data were, respectively, 234 BU (93.6 µg Der p 1) in the adult group and 217 BU (86.8 µg Der p 1) for the children.

Clinical improvement: The mean decrease between the baseline and final scores in the overall sample was significant for the nasal symptoms (12.1 ± 27.5 , $p = 0.04$), the ocular symptoms (5.2 ± 11.8 , $p = 0.02$), the total symptoms (19.0 ± 39.0 , $p = 0.03$) and the combined symptoms and medication score (23.9 ± 41.8 , $p = 0.005$). Statistical significance was almost achieved for the item "medication usage" (7.5 ± 16.5 , $p = 0.06$). In the separate

analysis of the two age groups, statistically significant decreases were observed in medication usage (9.7 ± 15.3 , $p = 0.02$) and combined symptoms and medication (29.6 ± 46.5 , $p = 0.02$) in the adult group, and in the ocular symptoms (8.4 ± 13.3 , $p = 0.02$) in the case of the children.

As for the investigator's assessment regarding the clinical evolution of the patients after one year of sublingual immunotherapy, 84% of the patients (76% in the children and 95% in the adult group) were considered to be improved or much improved as compared to their baseline clinical situation.

Safety: A total of 19 reactions occurred in five patients. It is noteworthy that 11 of these reactions occurred in one single patient (even though all of them were mild and none was cause enough for a modification of the dosage, the reiterative occurrence caused the patient to drop out from the study). All but one of the reactions occurred during the dose-increase phase. Figure 1 illustrates the adverse reactions in relation to the vial causing them. Among the total number of reactions, 3 were classed as local and 16 as systemic; the latter are described in Table III. The time of occurrence of the reactions is summarised in Figure 2. In relation to the total number of doses administered, the percentage of reactions was 0.38 (0.35 for the adults

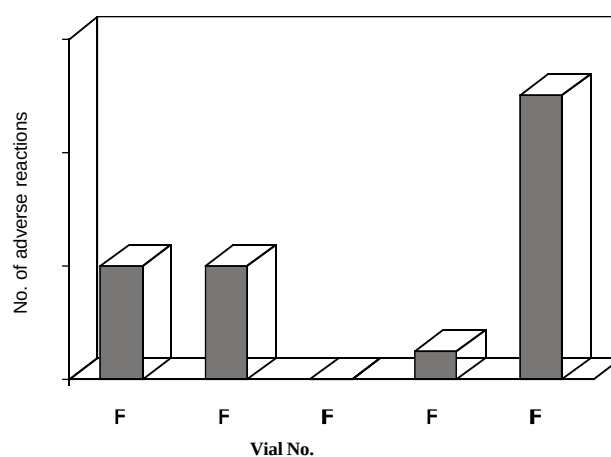


Fig. 1. Adverse reactions, per vial.

Table V. Degree of compliance with the protocol

Parameter assessed	Age group	Degree of compliance (%)		
		Very Good Good	Moderate	Bad/Very Bad
Follow-up cards (SLIT)	Adults	63.2	36.8	0
	Children	65.5	19.2	15.3
	Overall	64.4	26.7	8.9
Control cards (Symptoms/Medication)	Adults	88.3	11.7	0
	Children	45.8	29.2	25
	Overall	63.5	22	14.5
Attended the control visits	Adults			91.2
	Children			89.2
	Overall			90.1
Overall assessment (Investigator)	Adults	73.7	26.3	0
	Children	70.8	20.8	8.3
	Overall	72.1	23.3	4.6

and 0.4 for the children). Table IV details these findings.

Compliance: First and foremost, it should be stressed that the total number of dropouts observed during the treatment phase, representing 11.5% of the patients, is a normal and usual one for a one-year follow-up^{12,13}.

As regards protocol compliance, this was considered by the clinicians to be good or very good in 72% of the cases (71% in children, 74% in adults). Table V details the percentages for each of the items considered in the compliance assessment.

After completing the first year of immunotherapy, each patient completed a questionnaire with 15 questions, in which he gave his critical opinion regarding the SLIT therapy and the control and follow-up measures applied. Favourable responses were scored as "1" and unfavourable

ones as "0". The median scores achieved were 11 points in the children group and 10 in the adult one (10.5 in the overall sample, out of a possible maximum score of 15 points), expressing a favourable opinion from the patients. Furthermore, a statistically significant correlation existed between having a favourable opinion towards the treatment and having had good or very good protocol compliance.

DISCUSSION

The therapeutic use of sublingually administered allergenic extracts is progressively increasing. To this increase the considerable number of double-blind studies confirming the efficacy and safety of this route of administration has doubtlessly contributed.

In contraposition to the subcutaneous route, with which the patient must go to the specialist's clinic or at least to a Health Care Centre for administration of the treatment doses, in the case of the sublingual one the patient administers himself the treatment dose at his own home. Because of this, and also because this is a rather protracted therapy, it is unavoidable to establish mechanisms allowing the specialist, in the usual conditions of his everyday clinical practice, to assess not only the efficacy and safety of the therapy but also that the patient is adequately complying with it. Only in this way may the desired therapeutic success be achieved.

In the present study, which was carried out both on children and on adults, the degree of efficacy achieved both in

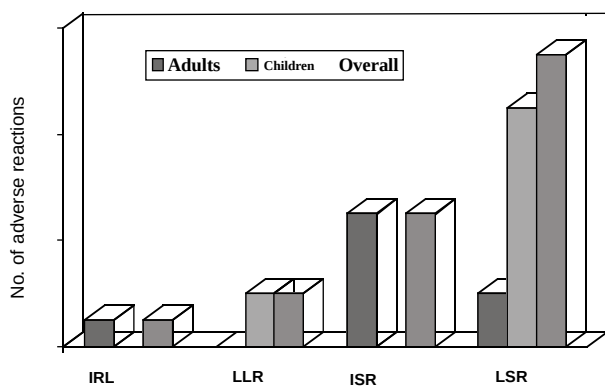


Fig. 2. Time of occurrence of adverse reactions (overall and per age group). IRL=immediate local reaction; LLR = late local reaction; ISR = immediate systemic reaction; LSR = late systemic reaction.

the decrease of the symptom scores and in the decrease of the use of medication has been fully satisfying both in the overall sample and in the adult patient group. This degree of efficacy, however, was smaller in the children group, possibly because their baseline clinical situation was better: their baseline total symptoms score was 54.5, vs. 79.1 in the adult group.

Regarding safety, the observed proportion of adverse reactions per dose was higher than that found in pharmacovigilance studies with this same therapy^{7,8}, possibly because there was one patient who did not tolerate this treatment well (as over one-half of the adverse reactions occurred in this one patient). However, all these adverse reactions remitted spontaneously and did not require any modification of the dosage or schedule.

As for the degree of compliance, and considering all the systems available for its assessment, both direct (use of biologic markers, quantification of drug concentrations in biologic fluids, etc.) and indirect (satisfaction questionnaires, completion of daily usage or clinical response diary cards), it is our considered opinion that the latter ones are those that may be most useful in clinical practice. In the present study it was seen that adequate compliance with the follow-up protocol, which was achieved in a considerable proportion of the patients, correlated well with having a favourable opinion about the therapy.

Thus, and in the light of the results presented, we conclude that the administration of sublingual immunotherapy (SLIT) to patients with allergic disease due to *Dermatophagoides pteronyssinus* sensitization represents an effective and safe therapeutic modality with a high level of patient compliance.

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