

Tolerance of a *Salsola kali* extract standardized in biological units administered by subcutaneous route. Multicenter study

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ABSTRACT

Background: Sensitivity to *Salsola kali* is a frequent cause of allergic respiratory disease in various regions of Spain. However, there are very few articles in which this allergen has been studied.

Methods and Results: In order to evaluate the tolerance of this extract, a prospective study has been performed. This study was observational, multi-centred and open, involving 88 patients with allergic respiratory disease due to sensitivity to *Salsola*, aged between 5 and 52 years. The administration of the extract was performed subcutaneously, through one of two treatment schedules: cluster (8 doses in 4 visits) or conventional (13 doses in 12 visits). A total of 42 adverse reactions were registered, in 26 patients (35 local reactions in 21 patients and 7 systemic reactions in 6 patients). Among the 7 systemic reactions, 4 were registered with the cluster protocol and 2 with the conventional protocol ($p = 0.329$). In no patients were serious adverse reactions registered.

Conclusion: The subcutaneous administration of a *Salsola* extract is safe and well tolerated, both when administered using a conventional schedule and when using a cluster schedule.

Key words: Subcutaneous immunotherapy. *Salsola*. Tolerance. Cluster schedule. Conventional schedule. Asthma. Rhinitis. Adults. Children.

RESUMEN

Antecedentes: La sensibilización a *Salsola kali* es una causa frecuente de enfermedad alérgica respiratoria en varias zonas de España. Sin embargo, apenas existen publicaciones en las que se estudie este alérgeno.

Métodos y resultados: Para valorar la tolerancia de este extracto, se ha realizado un estudio prospectivo, observacional, multicéntrico y abierto, en el que se han incluido 88 pacientes, de edad entre 5 y 52 años, con enfermedad alérgica respiratoria por sensibilización a *Salsola*. La administración del extracto se ha realizado por vía subcutánea, mediante dos esquemas de tratamiento: agrupada (8 dosis en 4 visitas) o convencional (13 dosis en 12 visitas). Se han registrado un total de 42 reacciones adversas en 26 pacientes (35 locales en 21 pacientes y 7 sistémicas en 6 pacientes). De las 7 reacciones sistémicas, 4 se registraron con la pauta agrupada y 2 con la convencional ($p = 0,329$). No se registró ninguna reacción adversa grave.

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Conclusión: La administración subcutánea de un extracto de *Salsola* es segura y bien tolerada, tanto cuando se administra con una pauta convencional como con una pauta agrupada.

Palabras clave: Inmunoterapia subcutánea. *Salsola*. Tolerancia. Pauta agrupada. Pauta convencional. Asma. Rinitis. Adultos. Niños.

INTRODUCTION

The *Chenopodiaceae*, the family to which the *Salsola* pertain, are an important cause of polynosis in different geographic zones of Spain (Levante, Aragón, Andalucía). In a epidemiological study published in 1995 of a sample of more than 4000 patients with allergy in Spain¹, the prevalence of sensitivity to *Salsola* pollen reached figures that oscillated between 8.9 % and 34.5 %, depending on geographical area.

Despite these figures, no study has addressed the possible use of immunotherapy with pollen of *Salsola*, as indicated by revising the literature between the years 1989 and 2002. The only reference that has been found is that presented at the European Academy of Allergology Congress celebrated in Rhodes in 1997, in the of Clinical Immunology section, in which the tolerance to two extracts was evaluated: *Salsola* and *Alternaria*².

For this reason, we carried out the multi-centre study presented here, with the aim of evaluating dose by dose the tolerance to an extract of *Salsola kali*. The extract was administered subcutaneously in patients with allergic respiratory disease that were only sensitive to this pollen. In order to adequately evaluate tolerance, the treatment was administered under the direct supervision of a specialist, using two frequently used therapeutic regimes in the initiation phase. The first regime consists of a conventional protocol of 13 doses, administering one dose each week. In contrast, the other consists of a cluster protocol, which has been previously evaluated in different studies³⁻⁵, in which the maintenance dose is reached in 4 sessions by administering two doses in each of the visits during the initiation phase.

MATERIALS AND METHODS

Patients

A total of 88 patients have been included in this study, aged between 5 and 55 years. The criteria for

inclusion in the study were: clinical history of rhinitis and/or asthma due to sensitivity to *Salsola kali*, with a positive result in skin tests (prick test BU *Salsola kali* 100 %, ALK-Abelló, S.A.) and/or a positive IgE to said allergen (CAP \geq class 2, Pharmacia, Uppsala, Sweden or > 0.7 KU/litre). The patients with relevant clinical sensitivity to other allergens, to whom it was impossible to administer the treatment under the supervision of a specialist, in those to whom immunotherapy had been administered with allergens in the 3 years prior to their inclusion in the study, or with a contraindication to the administration of the immunotherapy in agreement with the criteria of the WHO⁶, were all excluded from the study.

Ethical Aspects

All the patients that were included in the study gave their informed consent to participate, which was approved by the ethical committees of the centres implicated and by the relevant Health Authorities.

Design

This was a prospective, multi-centre, observational and open pharmacovigilance study.

Immunotherapy

A standardised extract of *Salsola kali* (25 BU/ml, Pangramin® Depot BU, ALK-Abelló, S.A.) was administered subcutaneously adsorbed in an aluminium hydroxide gel. The extract was administered, during the initiation phase, according to two possible treatment schemes as specified in table I: conventional and cluster. In this phase, the administration was performed on a weekly basis with an interval between doses, in the case of the cluster protocol of 30 minutes. In the maintenance phase, the administration of each dose was monthly. Since we are dealing with an observational study and in accordance with the legal requirements currently in force in Spain, each patient chose under which protocol that he/she wished the extract to be administered having previously been adequately informed.

All the doses were administered under the direct supervision of the specialist in the centres involved, in accordance with the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI)⁷.

No patient received premedication before any of the doses given in the study were administered.

Table I
Treatment schedule

Conventional				Cluster			
Week	Vial	Doses (ml)	BU	Week	Vial	Doses (ml)	BU
1	1	0.1	0.025	1	2	0.1/0.2	0.25/0.5
2	1	0.2	0.05	2	2	0.4/0.6	1/1.5
3	1	0.4	0.1	3	3	0.1/0.2	2.5/5
4	1	0.8	0.2	4	3	0.4/0.4	10/10
5	2	0.1	0.25				
6	2	0.2	0.5				
7	2	0.4	1				
8	2	0.8	2				
9	3	0.1	2.5				
10	3	0.2	5				
11	3	0.4	10				
12	3	0.6	15				
13	3	0.8	20				

Table II
Characteristics of patients

	n	%
Sex		
Female	47	53.4
Male	41	46.6
Age		
≤ 14 years	11	12.5
≥ 15 years	77	87.5
Diagnosis		
Rhinitis	69	78.4
Rhinitis and Asthma	19	21.6

Tolerance

Adverse effects were recorded in accordance with the guidelines of the EAACI⁷, both during the initiation phase as well as during the maintenance phase. The criteria used to adjust the doses were in the case of the conventional protocol in agreement with the recommendations of the EAACI⁷, whilst in the case of the cluster protocol action was taken in accordance to the experiences of previous studies³⁻⁵.

Statistical Analysis

Statistical analysis was performed using the statistical software package SPSS. The association be-

tween variables was determined using the chi-squared test or Fisher's Exact Test, establishing the level of significance at the probability of error < 0.5.

RESULTS

Characteristics of the sample

The principal characteristics of the sample are resumed in table II. The mean age of the patients was 28.1 ± 11.6 years and in 46.6 % of the subjects there was a family history of atopy. Over the whole duration of the study, a total of 4 patients dropped-out: two due to causes unrelated to the treatment; one patient for having presented two systemic reactions at the same dose, which in accordance to the experimental protocol meant the patient had to be retired from the study; finally a patient suffered an attack of eczema that led to the decision that the patient should no longer continue with the treatment.

Characteristics of the treatment

The administration of the treatment was carried out following the conventional protocol in 22 patients (25 %) and the cluster protocol in 66 (75 %). During the initiation phase, a total of 814 doses were administered, of which 528 corresponded to the cluster protocol and 286 to the conventional.

Tolerance

Local reactions: a total of 35 reactions were registered (4.3 % of the doses administered), of which 18 occurred during the administration of the cluster protocol (3.4 % of the doses) and 17 with the conventional protocol (5.9 %). The reactions were registered in 21 patients (23.9 % of the total number of subjects). Of the total number of reactions, 27 were registered in patients older than 15 years of age and 8 in younger subjects.

Systemic reactions: there were a total of 7 systemic reactions (0.86 % of the total number of doses administered), that occurred in 6 patients (6.8 %). These reactions are described in more detail in table III. No statistically significant differences were detected when the percentage of systemic reactions in each of the protocols used was assessed (0.7 % with the conventional and 0.76 % with the cluster protocol $p = 0.273$).

Table III
Description of systemic reactions

Type	Severity (EAACI)	Time of onset	Treatment phase	Treatment schedule	Vial	Dose (ml)
Fever	Grade 1	Delayed	Initial	Conventional	2	0,8
Urticaria*	Grade 3	Delayed	Initial	Cluster	3	0,1 + 0,2
Eczema	Grade 1	Delayed	Initial	Conventional	1	0,1
Asthma	Grade 2	Delayed	Initial	Cluster	3	0,1 + 0,2
Urticaria and angioedema	Grade 3	Delayed	Initial	Cluster	2	0,4 + 0,6
Cough	Grade 2	Delayed	Maintenance		3	0,8

*In this patient, according to the protocol, the dose was reduced twice. When the dose that provoked the reaction was again administered, the patient suffered an identical reaction and he was excluded of the protocol.

Although the systemic reactions appeared more often in patients that had suffered from asthma and rhinitis (10.5 %) than in those that were diagnosed exclusively with rhinitis (5,8 %), these differences were not statistically significant ($p = 0.273$)

Finally, when the appearance of adverse reactions was analysed in terms of age group, it is noteworthy that of the 7 systemic reactions registered, 2 appeared in 2 patients older than 15 years of age, and 5 occurred in paediatric patients (≤ 14 years), this difference being statistically significant ($p = 0.002$).

DISCUSSION

In general, immunotherapy studies have been centred on those allergens that have an elevated prevalence in any population, as is the case for mites or grasses. However, there are other allergens to which an important number of patients are sensitive, although this sensitivity may be restricted to particular geographic areas. For this reason, it is at times complicated to find reference in the literature to the behaviour of this type of allergen. This is indeed the case of *Salso*, which in zones such as Aragón, Levante or Andalucía (south and eastern Spain) is frequently the cause of allergic sensitivity, yet no references to this allergen exist in the literature.

In this study, we have focused our efforts on understanding the tolerance to this allergen. The allergen was administered under one of two distinct protocols, both frequently used by specialists: the conventional protocol or the cluster protocol. Given the characteristics of the study, each patient was allowed to choose under which of the two protocols he/she wished to have the treatment and administered. As such, it is notable and of interest that a significant percentage of the patients decided to admin-

ister the allergen following the cluster protocol. This protocol, involves an important reduction in the number of visits with respect to the conventional protocol, and in the doses necessary in order to reach the maintenance treatment. Several recent studies have justified the use of this type of protocol in clinical practice^{3-5,8-9}.

When we centred our attention on the systemic reactions, we could compare the results obtained with the cluster protocol to those obtained in other studies in which a similar or identical cluster protocol has been applied to administer pollen extract. Thus, in our study we find a similar relationship between the induction of a systemic reaction and the doses, or the numbers of patients, (0.76 % and 6.1 %) as that obtained in other studies. Indeed, Moreno et al² determined percentages figures of 1.2 % of the doses and 9.5 % of the patients, whilst in the study of Guardia et al³ these percentages were 0.9 % and 6.3 %, respectively.

Furthermore, it is important to underline that we did not observe any significant difference in the tolerance between those patients treated with the cluster protocol or those treated with the conventional protocol. Nevertheless, the cluster protocol must still continue to be administered under the strict control of a specialist, given that the administration of various doses on the same day could represent a risk to the patient. However, using the cluster protocol represents an important saving with respect to the conventional protocol, which can be coupled to the fact that in none of the studies performed to date has a difference been detected in terms of the severity of the reactions when these two treatment regimes are used.

Immunotherapy is clearly more efficient when acting in the early stages of an allergic illness. In this sense, its use in paediatric patients is clearly appro-

priate, not only from the curative point of view but also from the preventive point of view, as clearly demonstrated in other studies^{10,11}. Whilst in this study we did not set out to establish the levels of tolerance with respect to age, they did appear to be significantly more reactions in children than in adolescents or adults. For this reason, the administration of immunotherapy to infants should be very carefully supervised by specialists. However, it is important to underline that of the reactions that appeared in children, two were non-specific reactions: in one case fever and in the other case the reaction consisted of a non-pruriginous cutaneous eruption. In both cases, immunotherapy was administered under the conventional protocol and the patients continued with the treatment administration. The same occurred in a third subject that reacted with grade 2 asthma. In accordance with the protocol, once the doses had been lowered and subsequently returned to the original higher doses, the patient did not suffer any further reaction.

In conclusion, immunotherapy with an extract of *Salsola kali* is well tolerated in patients with allergic respiratory illness, either when administered in a conventional manner or when using the cluster protocol.

ACKNOWLEDGEMENTS

We wish to thank Santiago Martín, of the medical Department from ALK-Abelló, S.A. for carrying out the statistical analysis.

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