

Evaluation of paediatric tolerance to an extract of *Alternaria alternata* under two treatment regimes. A multicentre study

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ABSTRACT

In order to evaluate the efficacy and safety of an extract of *Alternaria alternata* in a paediatric population, a two phase study plan has been elaborated that in the first place consists of a retrospective analysis of tolerance under the standard treatment regimes used by the clinical groups involved. This was achieved by analysing the records of 94 patients that have been treated with this extract, these being consecutive patients included at 7 clinics over a period of 6 months. Two regimes were used: a conventional short regime of 7 doses and a cluster regime.

Under neither of these two regimes were any serious reactions registered. The percentage of local reactions was significantly greater using the short conventional regime than with the cluster regime (1.9 % and 0.4 % respectively, $p = .035$). In contrast, no significant differences were observed with respect to the systemic reactions (0.5 % and 1.2 %), these percentages also being similar to those registered with other extracts in which identical regimes have been used.

In conclusion, we can confirm that a very satisfactory tolerance profile was observed, with the advan-

tage that through using shorter regimes than the conventional regime of 13 doses, a considerable saving is made both in the number of visits and the doses necessary to reach the maintenance dose

Key words: *Alternaria*. Children. Immunotherapy. Rhinitis. Asthma. Moulds.

RESUMEN

Con el fin de evaluar la eficacia y la seguridad de un extracto de *Alternaria alternata* en una población pediátrica, se realizó un plan de estudio en dos fases, que consistió en primer lugar en un análisis retrospectivo de la tolerancia bajo las pautas de tratamiento convencionales empleadas por los grupos clínicos estudiados. A este fin se analizaron los historiales de 94 pacientes que habían recibido tratamiento con este extracto. Se trataba de pacientes consecutivos tratados en 7 clínicas durante un período de 6 meses. Se emplearon dos pautas: una pauta breve convencional de 7 dosis y una pauta agrupada o "cluster".

No se observaron reacciones de consideración bajo ninguna de las dos pautas. El porcentaje de reacciones locales fue significativamente superior al usar la pauta breve convencional que al usar la pauta agrupada (1,9 % y 0,4 % respectivamente, $p = 0,035$). En cambio, no se observaron diferencias significativas en lo relativo a reacciones sistémicas (0,5 % y 1,2 %), siendo estos porcentajes similares a los obtenidos con otros extractos y siguiendo pautas idénticas.

En conclusión, podemos confirmar la observación de un perfil de tolerancia muy satisfactorio, con la

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ventaja de que con pautas más breves que la convencional de 13 dosis se obtiene un ahorro considerable tanto en número de visitas como en las dosis necesarias para llegar a la de mantenimiento.

Palabras clave: *Alternaria*. Asma. Inmunoterapia. Hongos. Niños. Rinitis.

INTRODUCTION

The prevalence of sensitivity to fungi varies widely from one country to another. Hence, in a study performed on subjects with nasal and/or bronchial symptoms of a possible allergic aetiology¹, positive skin reactions to these allergens (specifically *Alternaria* and *Cladosporium*) oscillated between 3 % in Portugal (the lowest) up to 20 % in Spain (the highest figure). Perhaps it is due to this variability that there are relatively few studies that have focused on using immunotherapy with fungi. In the specific case of *Alternaria*, when a review of MEDLINE was performed, only five relevant studies were identified²⁻⁶. For this reason, the Spanish Society of Clinical Immunology and Paediatric Allergology (SEICAP), through its immunotherapy committee, decided to adopt a programme of clinical research with the objective of adequately documenting the tolerance and efficacy of treatment with an extract of *Alternaria* for allergic respiratory diseases due to sensitivity to this allergen in the paediatric population. The programme was established in two phases. In the first of these the tolerance to different treatment regimes was to be evaluated and in the second, according to the results obtained in the initial phase, the efficacy of using the extract was to be assessed through a double-blind trial designed to compare the effects of the extract against a placebo. In the current study, we present the results of the first phase in which an open, retrospective multicentre study has been set up to evaluate the tolerance to distinct treatment regimes.

MATERIALS AND METHODS

Patients

A retrospective analysis was carried out on the data corresponding to 94 patients from a total of 7 clinical groups, whose characteristics are laid out in table I.

The mean age of the patients was 9.6 ± 3.1 years (interval of 4-16 years) and the mean time over which

Table I
Characteristics of patients

| | n | % |
|-------------------|----|------|
| Sex | | |
| Male | 63 | 68.5 |
| Female | 29 | 31.5 |
| Diagnosis | | |
| Rhinitis | 6 | 6.5 |
| Asthma | 26 | 28.3 |
| Rhinitis & Asthma | 60 | 65.2 |

the allergic disease evolved was 4 ± 2.5 years (interval of: 1-15 years).

Immunotherapy

All the patients were treated with an extract of *Alternaria alternata* 100 % (Pangramin® Depot-UM, ALK-ABELLÓ, S.A., Madrid, Spain). This is an allergen extract standardized in biological units and assessed in mass units, with the major allergen Alt a 1 quantified in $\mu\text{g/ml}$. The maximum dose is 0.8 ml of the maximum concentration vial, equivalent to 0.2 μg of Alt a 1.

Patients followed two initiation regimes: 42 (44.7 %) followed a short conventional regime and 52 (55.3 %) a cluster regime. The characteristics of both treatment schedules are summarized in table II.

The total number of doses from which information was compiled was 952, of which 735 corresponded to the build-up phase of the doses, and 217 to the maintenance phase. Of the 952 doses, 392 were administered according to the conventional short regime and 570 with the cluster regime.

Table II
Treatment schedules

| Day | Short conventional | | | Cluster | | |
|-----|--------------------|------------|-----------------------|---------|------------|-----------------------|
| | Vial | Doses (ml) | μg Alt a 1 | Vial | Doses (ml) | μg Alt a 1 |
| 1 | 2 | 0.2 | 0.005 | 2 | 0.1/0.2 | 0.025/0.05 |
| 14 | 2 | 0.4 | 0.01 | 2 | 0.4/0.6 | 0.01/0.015 |
| 21 | 2 | 0.8 | 0.02 | 3 | 0.1/0.2 | 0.025/0.05 |
| 28 | 3 | 0.1 | 0.025 | 3 | 0.4/0.4 | 0.1/0.1 |
| 35 | 3 | 0.2 | 0.05 | | | |
| 42 | 3 | 0.4 | 0.1 | | | |
| 49 | 3 | 0.8 | 0.2 | | | |

Interval between doses in cluster schedule: 30 minutes.

All the doses were administered in the centres implicated in the study under the direct supervision of the specialist involved.

Statistical analysis

The statistical analyses were performed with the statistical software package SPSS. The association between variables was assessed using Fisher's exact test, establishing the level of statistical significance at a probability of error < 0.05.

RESULTS

A total of 18 adverse reactions were registered in 9 patients (9.6 % of the total number of patients), which represents the proportion of 1.9 % of the doses administered.

Local reactions: a total of 9 local reactions (0.95 % of the doses) were registered in 5 patients (5.3 % of the sample). All of these but one were observed 30 minutes after the administration of the allergen. Analysing these reactions with respect to the treatment schedule, seven local reactions were registered in 4 patients treated under the short conventional schedule, which represents 1.8 % of the doses administered and 9.5 % of the patients. In the case of the cluster regime, 2 local reactions were observed in a single patient, which represents 0.4 % of the total number of doses and 1.9 % percent of the total number of patients treated with this protocol. Hence, there is a statistical a significant difference in the number of local reactions per doses between the two treatment regimes ($p = 0.035$).

Twelve systemic reactions were registered and occurred with the administration of 9 doses (0.95 %) in 5 patients (5.3 % of the sample). In this case, 8 of the reactions were delayed and 4 were immediate. The description of these reactions can be seen in table III.

With respect to the number of patients, 2 of those treated with the conventional short regime suffered

systemic reactions (4.8 %), whereas these were registered in 3 patients (5.8 %) treated with the cluster regime. Hence, there was no significant difference in the number of patients that suffered systemic reactions between these two treatment regimes. If we consider the patients by age group, 2 patients of less and seven years of age suffered systemic reactions (7.4 %), whilst among those between eight and 14 years of age, this number rose to 3 (4.8 %). Again this difference was not statistically significant.

If we performed the same analysis when considering the number of systemic reactions per dose rather than per patient, we found that there were no significant differences between the two regimes. With the conventional regime there were 3 systemic reactions in 2 doses (0.5 %), whilst with the cluster regime there were 9 reactions with 7 doses (1.2 %). When grouped by age, the percentage of systemic reactions was identical between those subjects under 7 years of age, and those between 8 and 14 years of age (1 % in both cases).

Finally, the same number of systemic reactions was registered with the less concentrated and the more concentrated vials of allergen (6 in each case). All the reactions that required treatment, 9 in total, rapidly reverted with adequate attention. In no case was the use of adrenalin necessary and only 1 patient had to be taken off the treatment. This patient suffered an attack of asthma with rhinitis within 30 minutes of administration of the first dose in the cluster regime. The reaction responded to the treatment offered and the patient was given an appointment for the following week at which he was given 0.05 + 0.05 ml, after which he suffered a late episode of asthma, and for this reason the immunotherapy was suspended.

DISCUSSION

A research programme has been elaborated in collaboration with the Spanish Society of Clinical Immunology and Paediatric Allergies (SEICAP), to test the tolerance and efficacy of immunotherapy with an extract of *Alternaria alternata*. Within this plan, the initial study set out to review the data available regarding the tolerance of the patients sensitive to the allergen, and to analyse the information that was collected when the extract was administered in two different treatment regimes commonly used by the clinical groups involved in the study of these patients. Once analysed the most appropriate of the two treatment regimes, according to the results obtained here, will be evaluated for its efficacy in a double-blind, placebo-controlled study.

Table III
Systemic reactions: description

| Reaction | n |
|-----------|---|
| Cough | 4 |
| Rhinitis | 2 |
| Eczema | 2 |
| Urticaria | 1 |
| Asthma | 3 |

If we first consider the analysis of the results obtained, we find that the tolerance profile to the extract was very satisfactory. Independently of the regime used, no severe reactions were registered and all the subjects that required treatment responded to it rapidly and readily.

If we consider each regime separately, we find that in the first place, the short conventional regime registered a significantly higher number of local reactions than were encountered with the cluster regime. This data is in agreement with that found previously when analysing tolerance to a mite extract under the same cluster regime⁷ and with a conventional regime of seven doses⁸.

With respect to the systemic reactions per patient, no significant differences were observed between either regime and indeed, the percentages were practically identical in both (4.8 % with the conventional short regime and 5.8 % with the cluster regime). When the systemic reactions are analysed in terms of the doses administered, although the percentage found in the cluster regime (1.2 %) was greater than that found in the conventional short regime (0.5 %), the difference did not prove to be statistically significant ($p = 0.328$).

It is possible to compare the results obtained with this extract to those obtained in other studies in which tolerance to different extracts administered using the same treatment regimes has been analysed. In this case, we find that when administered under the conventional regime of seven doses, the percentage of systemic reactions with the *Alternaria* extract was identical to that registered with a mite extract⁸. When considering the cluster regime, the percentage was similar to that registered with an extract of olive and/or grass^{9,10}, and it was superior to that registered with the mite extract⁷. Therefore, it appears that the tolerance profile to the extract of *Alternaria alternata* does not differ substantially from that of other allergens such as mites or grasses.

A study published by Moreno et al¹¹ examined the tolerance to an extract of *Alternaria tenuis* administered at an identical concentration to that used here. In that study, tolerance to 4 different cluster treatment regimes was analysed in 108 patients that received 944 doses. In this case only two systemic reactions were registered.

In accordance with the results obtained, we can conclude that the tolerance profile to an extract of *Alternaria alternata* administered in a paediatric population is satisfactory. Furthermore, the use of treatment regimes that slightly reduce the number of

doses and visits necessary in order to reach the maintenance dose, with respect to the conventional regimes, will notably reduce the indirect costs inherent to the administration of immunotherapy.

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