Original Article

# Tolerance of a cluster schedule with a house dust mite extract quantified in mass units: multicentre study

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**Summary.** The standardisation of allergenic extracts in micrograms of the major allergen has encouraged the search for new treatment schedules, with the purpose of shortening the number of visits and doses required to reach the maintenance dose without eliciting a greater risk of adverse reactions for the patients.

With this objective, a prospective multicentre pharmacovigilance study was designed that included 200 patients with allergic rhinoconjunctivitis and/ or allergic asthma sensitised to mites (Dermatophagoides pteronyssinus and/or farinae). The dose increment period was carried out using a cluster schedule, where the optimal dose was reached after 4 visits, administering two doses in each visit. The duration of the study was 5 months and a total of 1902 doses were administered.

At the end of the trial, 31 adverse reactions in 23 patients were recorded. Six of these were systemic (0.3% of the administered doses) recorded in 6 patients (3% of the sample). One was an immediate reaction (grade 1) and 5 delayed (4 mild and 1 moderate). Two were asthmatic exacerbations, 2 cutaneous reactions, 1 rhinitis and 1 an unspecific symptom (not IgE-mediated). Two appeared upon administration of the first vial and the remaining 4 after administration of the third cluster.

Therefore, the schedule tested presents an adequate tolerance profile, suggesting savings (compared to the conventional schedule of 13 doses per patient) of 1800 visits and 1000 treatment doses in the whole study.

**Keywords:** Rhinoconjunctivitis, Asthma, Cluster Immunotherapy, Pharmacosurveillance, Mites.

## Introduction

Subcutaneous immunotherapy is normally administered during a build-up phase, using treatment regimes that start with low concentrations of the allergen with one dose per week, and reaching the maintenance dose after a period that usually varies between 12 and 15 weeks. This form of treatment, endorsed by a large number of clinical trials testing safety and efficacy, has as its fundamental objective to induce in the patient a progressive tolerance to the allergen responsible for setting off the allergic process during the initiation phase, considered as the phase with the greatest risk of adverse reactions. The purpose of this is to reach the maintenance or therapeutically effective dose, capable of interfering with the immunopathological mechanisms of the allergic disease, with the least possible adverse effects.

However, in the 80's, especially in patients with an allergy to Hymenoptera venom, new more aggressive treatment methods were developed in which the optimal treatment dose was reached within a period as short as hours, thus avoiding the life-threatening risk implied

from a new sting from these insects in unprotected patients [1, 2]. Using these new treatment schedules, less aggressive alternative methods were sought that would also enable the reduction in the time, compared to conventional methods, needed to reach the optimal dose. These rules were named cluster rules [3, 4].

It was at the end of the 80's and particularly during the last 10 years that different authors considered applying these types of cluster rules in immunotherapy with pneumoallergens for respiratory allergy, such as those mentioned in the review published by Parmiani et al. [5]. However, in many cases too few patients were included, which without a doubt makes it difficult to draw conclusions regarding the tolerance of the schedule tested. On the other hand, the different allergenic pressure, according to geographical area, may have as consequence the finding of different tolerance profiles on a same treatment schedule.

The present multicentre study was conducted with the objective of evaluating the tolerance of a cluster schedule in patients with respiratory allergic disease due to sensitisation to mites. This study is set within a general work plan in which the same schedule has been tested for seasonal allergens (Olea europea and/or mixture of grasses) [6].

## Material and Methods

### Patients

A total 200 patients were included in 8 clinical groups. The inclusion criteria were: clinical history of rhinitis and/or perennial allergic asthma due to sensitisation to mites (Dermatophagoides pteronyssinus and/or farinae) with at least 1 year's duration, with positive cutaneous (skin prick test to D.pteronyssinus and/or farinae, ALK-ABELLÓ, 100 BU/ml, wheal diameter > 5 mm) and/or specific IgE in serum tests (≥ class 2, CAP Pharmacia, Uppsala, Sweden). Excluded from the study were those patients who had received previous immunotherapy, were sensitised to other clinically relevant allergens, could not receive the treatment under the supervision of an allergist, or those in whom the administration of immunotherapy was contraindicated according to the WHO criteria [7].

### Immunotherapy

The immunotherapy was administered subcutaneously using a vaccine of Dermatophagoides pteronyssinus and/or farinae (Pangramin® Depot-UM, ALK-ABELLÓ, S.A., Madrid, Spain). In both cases, the allergenic extracts were adsorbed onto aluminium hydroxide gel, biologically standardised and with their major allergens (Der 1 and 2) quantified in Mass Units, according to the methodology described by the manufacturer [8].

The treatment scheme during the increment dose phase followed a cluster rule, as shown in the Table 1 below. The interval between each dose was 30 minutes. Once the optimum treatment dose was reached (0.8 ml of the maximum concentration), as established in a previous study [9], the maintenance phase was carried out by the administration of the first dose 15 days after the end of the dose increment period, later doses being administered at monthly intervals. The duration of the treatment was 5 months.

All doses were administered under the supervision of a specialist at each one of the participating centres. The clinical situation of each patient before administering each dose was evaluated according to the recommendations of the EAACI Position Paper [10].

The rules followed for modifying the dose, whether for discontinuing treatment or for the appearance of adverse reactions, were identical to the ones used in a previous study [6]. In no case was premedication with

*Table 1.* Treatment schedule

| | | Doses | | |
|---|---|---|---|---|
| **Day** | **Vial (Concentration)** | **mL** | **BU** | **mg Der1/2** |
| 1 | 2 (100 STU/mL) | 0.1 + 0.2 | 0.1+0.2 | 0.04/0.02 + 0.08/0.04 |
| 7 | | 0.4 + 0.4 | 0.4+0.4 | 0.16/0.08 + 0.16/0.08 |
| 14 | 3 (1000 STU/mL) | 0.1 + 0.2 | 1+2 | 0.4/0.2 + 0.8/0.4 |
| 21 | | 0.4 + 0.4 | 4+4 | 1.6/0.8 + 1.6/0.8 |

The interval between doses was 30 minutes
STU= Standard Treatment Units

antihistamines used before administering the specific immunotherapy.

### Safety monitoring

The recording of adverse reactions was carried out according to the recommendations contained in the EAACI Position Paper [10].

The study was monitored by an electronic data collection system that processed the recorded data and generated "on-line" reports for consultation by all participating groups. The design of a private network and a secure system of personal codes guaranteed the confidentiality of the data at all times.

### Statistical analysis

The entire statistical analysis was performed with the SAS system, version 8.1. The association between the different variables was carried out by means of Fisher's exact test, calculating the 95% confidence intervals by the exact binomial method.

## Results

### Sample Characteristics

The characteristics of the 200 patients included in the study and of the treatment administered are summarised in Table 2.

### Tolerance

A total 31 adverse reactions in 23 patients were recorded. Of these, 25 were local and appeared in 18 patients, representing 1.3% of the administered doses and 9% of the sample. Of these 25 reactions, 9 occurred during the first 30 minutes after the administration of the vaccine and 16 were delayed; 72% occurred during the administration of the vial of maximum concentration (vial 3) and the remaining 28% during the administration of the first vial (vial 2).

Regarding systemic reactions, there was a total 6, representing 0.3% of the administered doses. These 6 reactions took place in 6 patients (3%). The descriptions of the reactions appear in Table 3. As for the cutaneous reactions, one was a minor reaction consisting of generalised pruritus and flare up at the injection sites that disappeared without requiring treatment. The second one was a reaction of moderate intensity, consisting of eruptions of vesicles in the face and neck, accompanied by fever and joint pain, that remitted spontaneously within 2 days of appearance. There were no significant differences as regards the vaccine used (3 with an extract of D. pteronyssinus and 3 with the mixture of D. pteronyssinus and D. farinae, representing a percentage of 2.6% and 3.6% respectively of the total patients treated with each extract), nor as regards diagnosis (3 reactions in patients with asthma (3.2%), and 3 in patients with the exclusive diagnosis of rhinitis (2.9%)). Neither was the age of the patient a risk factor, since one reaction appeared in a patient younger than 14 years (2.9%) and the remaining 5 delayed reactions appeared in patients over 22 years (3%).

As for the time of appearance, only 1 was an immediate reaction (grade 1 according to the EAACI classification), and 5 were delayed reactions. Of these, 4 were classified as minor and one of moderate intensity.

The most significant aspect concerns the vial and dose in which the systemic reactions were recorded. Two of the reactions occurred with the administration of the first vial (vial number 2). Both occurred as delayed reactions after the injection of the first cluster (0.1 + 0.2 ml). The percentage of these reactions with respect to the total patient doses administered was 1% (CI 95%: 0.12% - 3.51%). The remaining 4 occurred on administering the maximum concentration of vial 3. One was immediate after the 0.2 ml dose, and the remaining 3 appeared as delayed reactions after administering the first cluster of this vial (0.1 + 0.2 ml). The percentage of these 4 reactions in relation to the total number of

*Table 2:* Patient's characteristics

| | | N | % |
|---|---|---|---|
| Diagnosis | Rhinitis | 95 | 47.5 |
| | Asthma | 6 | 3.0 |
| | Rhinitis & Asthma | 99 | 49.5 |
| Age | ≤ 14 years | 34 | 17 |
| | ≥ 15 years | 166 | 83 |
| Doses administered: | | | |
| Total | | 1902 | |
| Initial phase | | 1497 | |
| Maintenance phase | | 405 | |

*Table 3:* Systemic reactions: description

| Type | n |
|---|---|
| Rhinitis | 1 |
| Asthma | 2 |
| Cutaneous | 2 |
| Unspecific symptoms | 1 |

patients who received the first 2 doses was 2.1% (CI 95%: 0.57% - 5.28%). Therefore, in neither case were statistically significant differences observed between the percentages of reactions occurring with the two vials that comprised the treatment.

## Discussion

In approaching the presented multicentre study, the main objective established was finding a cluster schedule that could serve as reference scheme for any patient with respiratory allergic disease with sensitivity to mites (Dermatophagoides pteronyssinus and/or farinae). To be able to fulfil this objective, a series of fundamental requirements existed all of which were accomplished. Firstly, the use of an appropriately standardized extract, with quantification of the majoritary allergens (Der 1 and 2) in micrograms per millilitre. In this way, the reproducibility of the results was ensured when administered by clinical groups other than those participating in the study. Secondly, the extract had a defined optimum maintenance dose [9] and its efficacy was confirmed by previous studies [11]. Lastly, there was a dose-by-dose control of the preparation tolerance, which should always be administered by allergists with experience in the handling of allergenic vaccinations.

To adequately value the tolerance of this new treatment scheme, it is fundamental to be able to compare these results with those published by other authors who, using identical extract and product, have carried out the administration of the treatment under a conventional scheme. In this sense, Tabar et al. [12] published a study in which 5120 doses were administered to 226 patients, with a percentage of systemic reactions per dose of 0.5%. In another similar study [13], in which the number of patients and administered doses were 88 and 1244 respectively, the percentage was 0.32%. As can be seen, these percentages are similar or even slightly higher than those recorded in the present study (0.3%). A characteristic common to these three studies was the absence of severe systemic reactions.

Likewise, in another study in which an appropriately standardized extract of mites was used and the administration of the dose was also carried out under a cluster rule [14], the percentage of systemic reactions per dose was significantly higher (0.87%).

One aspect that decisively influences the tolerance of the rule is the extract used. As shown in a previous study [6] carried out using pollen vaccines (a mixture of 5 grasses and/or Olea europaea) also measured in Mass Units, the percentages of systemic reactions per dose (1.2%), and per patient (9.5%), were higher than those found in our study.

Lastly, there is an important factor that should be considered when using this type of rules. If the 200 patients included had been administered the vaccine under the conventional scheme of 13 doses, the total number of visits and administered doses would have been 2600. With the rule proposed here, the savings in the number of visits and necessary injections to reach the optimal maintenance dose is 69% (1600 visits) and 38.5% (1000 doses) respectively.

Therefore, in view of the results obtained, we can conclude that the proposed cluster schedule under these administration conditions presents an excellent tolerance profile, with a percentage of systemic reactions even lower than with the conventional schedule. It also represents a savings in the number of visits and in the number of doses necessary to reach the maintenance dose.

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