

Tolerance of a Cluster Schedule on the Treatment of Seasonal Allergic Respiratory Disease with Pollen Extracts Quantified in Mass Units

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Summary. In order to evaluate the tolerance of a cluster schedule on specific immunotherapy (SIT), 306 patients were included in a multicenter study. The patients were suffering from rhinoconjunctivitis with/without asthma, caused by sensitization to olive and/or grass pollen. SIT was administered subcutaneously according to a cluster schedule in which the maintenance dose is reached after four visits (3 weeks). The extracts were biologically standardized with major allergens quantified in mass units.

Local reactions appeared in 7.2% of the patients and 1.3% of the doses. Systemic reactions (SR) were recorded in 1.2% of the doses administered to 9.5% of the patients. No anaphylactic shock was registered, and all the SR responded fully and rapidly to treatment. There was no difference in SR according to diagnosis or allergen extract used.

The majority of SR occurred with the administration of vial of higher concentration (Vial 2: 7 SR (22%), Vial 3: 32 SR (78%), $p < 0.05$). Of the 32 SR recorded with Vial 3, 13 (41%) were immediate, with no existing association between dose administered and appearance of SR. However, of the 18 delayed SR (56%), 14 occurred after the administration of the first two doses of Vial 3 and four occurred after administration of the second two doses (78% vs 22%, $p < 0.05$). On the other hand, this regime realized an important saving in cost and time compared to the conventional schedule (1581 fewer doses and 2754 fewer visits were necessary to reach the optimal dose).

Considering all these factors, the clinical profile of the proposed regime may be qualified as good. However, future studies are necessary in order to better adjust the schedule to avoid the delayed SR that occurred after the administration of the first two doses of Vial 3.

Keywords: cluster immunotherapy, olive, grasses, mass units, rhinitis, asthma

Introduction

Biological standardization of allergenic extracts began in the 1980s and the later quantification into mass units that permitted the safest and most effective allergen dose to be established in terms of μg of active ingredient, has propelled the development of new treatment programs using increasing dosages. Therefore, instead of conventional treatment programs in which treatment begins with very low doses of allergen that are increased in once-weekly administrations over periods ranging from 12 to 15 weeks, new programs have been developed characterized by: (1) Starting the treatment with higher doses than those recommended in conventional treatments, (2) administration of several doses in one day, and (3) larger differences between successive doses, reaching the maintenance dose in a much shorter time. This leads to an important series of advantages both for the patients and for the hospital departments or units where this kind of treatment is given. First, a reduction in the number of visits required reduces costs for both the patients and the health service, permitting improved management of the waiting lists. Second, the treatment can be started, in the case of seasonal allergens, nearer to the start of the pollen season; always, of course, suitably assessing the risk/benefit for the patient.

Three main types of therapeutic regimes have been developed: ultrarush, rush, and cluster. In the two former regimes, the maintenance dose is reached in a very short time, in days or even hours. Given that there is a greater risk of systemic reactions (SR) with these regimes, they have been used almost exclusively in patients with allergy to bee stings who are at risk of death from a subsequent sting. However, cluster regimes, less aggressive than the other two types because of the weekly interval between doses, have been used for both inhaled antigens such as mites [1–6], animal dander [7–8], molds [9–11], and mainly pollens [12–22], and also for venoms [23–29]. Several studies have also compiled the results obtained with different allergens [30–31].

However, in all these studies there is considerable variety in the regimes used, in relation to the duration of the regime (number of weeks), the dose administered at each visit, the type of extract used (aqueous, depot, and even allergoids), and the use (or not) of premedication [18, 20] to prevent side effects. Moreover, many of these studies

were carried out by one clinical team on a small number of patients, which makes it difficult to adequately assess the regime used.

For this reason, the present study was proposed, in which an important number of centers participate and a large number of patients are included, permitting the tolerance profile of a cluster regime to be measured satisfactorily. In this way, this regime can be established as a reference regime for the administration of pollen extracts for widespread use in the Mediterranean region.

Material and Methods

Patients

A total of 306 patients were included in 12 clinical groups. The inclusion criteria were: clinical background of rhinitis and/or seasonal allergic asthma by sensitization to the pollen of *Olea europaea* and/or grasses, at least one year's evolution with positive skin-prick tests, and/or specific IgE in serum ($\geq$ class 2, CAP Pharmacia, Uppsala, Sweden). Patients who had received previous immunotherapy, were sensitized to other allergens of clinical importance, or for whom the administration of immunotherapy was contraindicated in accordance to the WHO criteria [32], were excluded.

Immunotherapy

Immunotherapy was administered subcutaneously with extract of *Olea europaea* and/or a mixture of grasses (*Dactylis*, *Festuca*, *Lolium*, *Phleum*, *Poa*), Pangramin® Depot-UM, Alk-Abelló, S.A., Madrid, Spain. In both cases, these were allergenic extracts adsorbed in aluminium hydroxide gel, biologically standardized, and with the major allergens (Ole e1 and Group 5, respectively) quantified in mass units according to the methodology described by the manufacturer [33].

The treatment program during the increasing dosage phase in a cluster regime is shown in Table 1. The interval between doses was 30 minutes. The maintenance phase was carried out coseasonally with the first dose administered 15 days after the end of the increasing dose period

Table 1. Treatment schedule

Day	Vial (Concentration)	ml	BU	Doses	
				μg Ole e 1*	μg Group 5**
1	2 (100 STU/ml)	0.1 + 0.2	0.25 + 0.5	0.15 + 0.3	0.025 + 0.05
7		0.4 + 0.4	1 + 1	0.6 + 0.6	0.1 + 0.1
14		0.1 + 0.2	1.5 + 3	1.5 + 3	0.25 + 0.5
21	3 (1000 STU/ml)	0.4 + 0.4	10 + 10	6 + 6	1 + 1

The interval between doses was 30 minutes; *In treatments *Olea europaea* 100%, **In treatments grasses 100%

and the final doses at monthly intervals. The duration of the treatment was 5 months (March–July). This treatment schedule is used as routine treatment in the majority of centers participating in the study. For this reason, the informed consent of patients was not considered necessary.

All the doses were administered under supervision of a specialist in the centers participating in the study. The clinical situation of each patient, before administration of each dose, was assessed according to the instructions in the Position Paper of the EAACI [34].

Safety Monitoring

Adverse reactions were recorded in accordance with the classification contained in the Position Paper of the EAACI [34].

During the initial stage, the dose was modified according to the following program: in case of local reaction or nonspecific immediate reaction the regime was not modified. In the case of a systemic reaction of grade 2–3 immediately after administration of the first cluster dose, treatment was stopped on the same day. One week later the dose that triggered the reaction was reduced by half, and administered in duplicate with an interval between the two doses of 30 min. If this was well tolerated the treatment regime schedule was continued. If there was another systemic reaction, the patient was excluded from the study. In the case of a grade 2–3 immediate systemic reaction after injection of the second dose of the cluster or late systemic reaction, the last cluster administered was repeated again a week later. If this was well tolerated, the treatment program was continued. If not, the treatment was suspended.

Pretreatment with antihistaminic agents was not given in any case before administering the specific immunotherapy (SIT).

The study follow-up involved an electronic data collection system in which the data recorded were processed and “on line” reports were drafted to be consulted by all the participating groups. Confidentiality of the data was guaranteed at all times by a network with restricted access via personal passwords.

Table 2. Patients' diagnosis

Diagnosis	N	Patients
		%
Rhinitis (R)	20	48
Rhinoconjunctivitis (RC)	147	6.5
R and Asthma	19	37.6
RC and Asthma	115	6.2
Asthma	5	1.6

Statistical Analysis

All the statistical analysis was done using the SAS system, version 8.1. The association between different variables was done by the Fisher's exact test, and confidence intervals were estimated with a reliability of 95% by the exact binomial method.

Results

Patients

A total of 306 patients, 154 women and 152 men, with a mean age of 25.3 ± 9.8 years were included in the study. Of these, 21 (6.8%) did not finish the treatment. Twelve of these dropped-out of the treatment mainly because of the difficulty in leaving work to attend the centers to receive the immunotherapy (five patients) or due to the appearance of adverse reactions (two patients), described in the section on tolerance. The remaining patients who abandoned the trial did so because of: illness in one patient, changing residence in one, rejection of the regime once started in one, and in two cases the motives were unknown. Of the nine patients who were withdrawn from the study by the doctors, in eight cases this was because of adverse reactions as described in the section on tolerance.

The patients' diagnoses are recorded in Table 2. The mean time of evolution of the allergic disease was 6 ± 4.5 years.

Immunotherapy

A total of 3130 doses were administered, of which 2397 corresponded to the dose-increment phase and 733 to the maintenance phase.

In relation to the treatment given, for 102 patients (33.3%) an extract of grasses (100%) was used, for 44 patients (14.4%) an extract of *Olea* (100%) was used, and a 50% mixture of both extracts was used for the remaining 160 patients.

Tolerance

A total of 79 adverse reactions were recorded, corresponding to 2.5% of the total doses administered in 47 patients (15.4%). Of the 79 reactions, 40 were local, corresponding to 1.3% of the total doses administered, occurring in 22 patients (7.2%).

Regarding the SRs, that are described in Table 3, a total of 39 were recorded (1.2% of the doses administered) in 29 patients (9.5%). All except one occurred dur-

Table 3. Description of systemic reactions (SR) according to EAACI classification

Immediate SR		Delayed SR	
Unspecific symptoms	5	Unspecific symptoms	7
	0	Urticaria (U)	7
Mild Asthma	6	Asthma	2
Urticaria	4	Rhinoconjunctivitis	3
Angiodema	1	Angiodema (Ao)	2

+1 Urticaria not classified as immediate or delayed

ing the increasing dose phase. Therefore, the percentage of SR per dose during the initiation phase was 1.6%. Of the total SR, 16 (41%) appeared during the first 30 min after administration of the treatment, and their degrees of severity in accordance with the EAACI classification [34] were as follows: five (31%) were Grade 1, eight (50%) were Grade 2, and three (19%) were Grade 3. There were 22 late SRs, of which 15 (71%) were classified as mild, five (24%) as moderate, and one (5%) as severe. There was no case of anaphylactic shock.

In relation to the allergenic extract used, the SRs were distributed as follows. With a grass-extract 100%, 10 SRs occurred in nine patients (8.8%, CI 95%: 4.1–16.1). The percentage refers to the number of patients with reactions in relation to the total number of patients treated with the same extract. With an extract of *Olea europaea* 100%, 12 SRs appeared in seven patients (15.9%, CI 95%: 6.6–30.1), and with a mixture of both extracts, 17 SRs were recorded in 13 patients (8.1%, CI 95%: 4.4–13.5). There were no statistically significant differences either in the percentages of SR or in the percentage of patients, in spite of the fact that in the case of patients treated with an extract of *Olea* 100% the percentage of patients with reactions was double that recorded in patients treated with the grass-extract or with the mixture of both.

Table 4. Systemic reactions/vial

Vial:	2	3
No. SR:	7	32
IC95%:	7.5–33.5	66.5–92.5

$p < 0.05$

Table 5. Systemic reactions by vial and doses

Dose	Immediate				Delayed	
	0.1	0.2	0.4	0.4	Cluster 1 (0.1 + 0.2)	Cluster 2 (0.4 + 0.4)
SR vial 2			1	2	1	3
SR vial 3	3	6		4	14*	4*

* $p < 0.05$, Fisher's exact test

Studying the SRs in relation to the patient's clinical condition: 16 SRs were recorded in 14 patients without asthma and 23 SRs in 15 patients with asthma, although these differences were not significantly different. However, differences were observed in relation to *when* the reactions appeared since immediate reactions appeared significantly more often in patients with asthma than in those without asthma (15 SR vs 1 SR respectively, $p < 0.05$ Fisher's exact test). In the case of late reactions, although these appeared more frequently in patients without asthma than in those with this condition (15 and 8, respectively), these differences were not significant.

The analysis of the association between the SRs and the doses that caused them are recorded in Tables 4 and 5. As can be observed in Table 4, there were significantly more SRs after administration of Vial 3 than after administration of Vial 2 (Vial 3: 32 SR, 82.1%, CI 95%: 66.5–92.5; Vial 2: 7 SR, 17.9%, CI 95%: 7.5–33.5, $p < 0.05$, Fisher's Exact Test). If we analyze these reactions in relation to when they occurred and at which dose, there are significant differences between the late SRs recorded after administration of Vial 3, since these were more frequent after administration of the first cluster than after administration of the second cluster of this vial (Cluster 1 (0.1 + 0.2) Vial 3: 14 SR, 78%, CI 95%: 52.4–93.6; Cluster 2 (0.4 + 0.4) Vial 3: 4 SR, 22%, CI 95%: 6.4–47.6, $p < 0.05$, Fisher's Exact Test).

Discussion

Traditionally, subcutaneous administration of SIT treatment with allergens was based on the injection of gradu-

ally increasing doses, always starting with very low doses of allergen, 10–3 or 10–4 of the maximum dose. The procedure followed was often arbitrary and the most important objective was to guarantee the patients' safety.

However, since the biological standardization of allergenic extracts, several studies using depot extracts have demonstrated an absence of reactions during administration of the first treatment doses [35, 36]. In these studies, administration of the SIT was done by conventional treatment regimes. This absence of reactions has also been confirmed in subsequent studies in which a regime different to the conventional one has been used, administering several doses together on the same day [5, 22, 28]. On the other hand, several studies show that the administration of SIT with rapid regimes produces an early immune response in the patient [37]. Therefore, it seems reasonable when considering both the safety and the efficacy of SIT, to modify traditional forms of administration of this type of treatment and to look for alternatives that would also imply reduced costs derived from health care.

Among the possible alternatives to conventional schemes during the increasing dosage phase (ultrarush, rush, or cluster), which several clinical teams have been working on over the last few years, in the case of inhaled allergens, in which there is no life-threatening situation for the patient such as occurs with patients allergic to bee stings, the cluster regime appears to be the most suitable.

However, from the literature it can be seen that a wide range of different cluster regimes can be used [1–22]. Because of this great diversity, the present work aims to establish a clinical model of a cluster regime that can serve as a standard model for routine use in hospitals.

Logically, the first aspect to take into consideration is the tolerance to the regime. Although all the reactions recorded by the authors are included in the results, it is important to point out the number of SRs, specifically 12, which were nonspecific, nonIgE-mediated reactions such as hoarseness, tiredness, or numb limbs. It is always difficult to determine the precise association of this type of reaction with the treatment. If these reactions are excluded from the analysis, the number of SRs is reduced to 27 in 22 patients, corresponding to 0.8% of the total doses administered and to 7.2% of the patients. We consider it important to take these figures into account when assessing tolerance to the regime.

When these results are compared with those published by other authors for studies using similar extracts to those administered here but following a conventional treatment regime, we find that the percentage of SR is higher in the regime studied here. Hence, Tabar et al. [35] obtained an SR corresponding to 0.37% of the doses administered to 4.8% of patients and Horak [36] reported SR in only 1.2% of patients.

If we make comparisons with the results obtained by other authors using similar treatment regimes, we first observe that very few studies are comparable to the one analyzed here because of differences in the geographical re-

gion studied, the type of patients and, especially, the different manufacturers and compositions of the extracts used. A similar regime to that used here was only found in one recent study [22] in which 10 doses were administered in four visits with the same product (Pangramin® Depot-UM) and similar extracts: grasses, *Olea*, *Chenopodium*, and/or *Plantago*. A total of 139 patients were studied who were administered a total of 1433 doses. Seven adverse reactions (six local and one systemic) were recorded in seven patients, giving percentages of SR per dose and per patient of 0.07% and 0.7%, respectively. In other studies, however, the results obtained with the regime proposed here as compared to those obtained in other works suggests a good tolerance profile. Hence, Walker et al. [20], in patients with respiratory allergic conditions due to sensitization to *Gramineae*, using a regime in which the maximum dose was reached in 4 weeks (seven visits), and 12 late SRs were reported, nine in the increasing dose phase (four in the active group). This corresponds to 1.4% of SRs per dose. In that study, patients were premedicated with an antihistaminic agent before they were administered SIT. Nielsen et al. [18], with a regime in which the maximum dose was reached in 7 weeks using a depot extract of *Betula* or *Phleum*, obtained an SR percentage per dose of 5.8% in patients premedicated with Loratadine and of 9.5% in patients administered placebo before each SIT injection. This also occurred with Winther et al. [19], who used a similar regime using the same allergens but with aqueous extracts, and obtained an overall SR of 2% per dose, which rose to 3.3% in the case of patients treated with *Phleum*.

These data, together with the fact that all the reactions are rapidly and completely reverted on treatment and that all the patients who completed the study reached the maximum predicted dose (0.8 mL of the vial with the maximum concentration), implies that the proposed model has a clinical profile that can be considered as good. However, since there were 12 late SR after administration of the two first doses of Vial 3, we should continue working to improve the proposed regime. There are two possible reasons for the late reactions around the time of administration of the third cluster. Either the dose administered is too high, in which case this would be amended by reducing the dose. The other possibility is that the previous dose administered did not induce a sufficient tolerance level in which case the solution would be to increase the previous dose. Given the reduced number of reactions appearing after administration of the fourth cluster (0.4 + 0.4 of Vial 3), we consider the second explanation to be the most likely. However, there are other possibilities, such as to include an additional intermediate dose before the dose causing problems.

In this point, it is important to point out that all the doses were administered by qualified personnel under supervision of specialists in Allergy Services or Immunotherapy Units, in strict accordance to the EAACI recommendations. For this reason, we can consider that SR were

all due to dose effects, it being possible to exclude other risk factors as causes of these reactions. Although it is encouraging that no severe SR were observed in this study involving more than 300 patients, these data do not exclude the possibility of anaphylaxis, which is an extremely rare event. For this reason, further surveillance of large numbers of patients is needed.

One very interesting clinical finding was the percentage of patients treated with an extract of *Olea* 100% who presented SR. Whereas the percentage of patients with SR relative to the total number of treated patients was very similar in those treated with a *Gramineae* extract (8.8%) to those administered an extract of *Gramineae* + *Olea* (8.1%), in those treated with an extract of *Olea* 100% the percentage rose to 15.9%. Although this difference is not statistically significant, it is clinically relevant and could indicate that the same treatment regime may not be suitable for all the extracts. On the other hand, the study confirmed that immediate SR are more common in patients suffering from bronchial asthma.

Another interesting finding was that most of the maintenance doses were administered during the pollen season and only one late SR of moderate intensity appeared during this period.

Finally, there are several other factors that should be taken into account when studying the repercussions of this kind of regime. In the treatment regime studied here in 306 patients, 1581 fewer doses were used and 2754 fewer visits to the specialist, in comparison to the number of doses and visits that would be required for the same number of patients following the conventional treatment regime of 13 doses to reach the maintenance phase.

In conclusion, the regime with two doses per visit and four visits required to reach the maintenance dose has presented a good degree of tolerance and implies a large reduction in costs relative to the conventional treatment regime.

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