Retrospective study of tolerance to short initiation schedules in subcutaneous immunotherapy

B. Gandarias[1], Mª D. Alonso[2], M. Fernández Rivas[2], L. Fernández-Távora[3], P. Miranda[4], D. Muñoz Lejarazu[5], M. Sotillo[6], J. Tejero[7], P. Rico[1]

[1] ALK-ABELLÓ, S.A. Madrid, Spain, [2] Fundación Hospital Alcorcón. Madrid, Spain, [3] C.P.E. Virgen de la Cinta. Huelva, Spain, [4] Private Clinic. Córdoba, Spain, [5] Hospital Santiago Apóstol. Vitoria, Spain, [6] Private Clinic. Sevilla, Spain, [7] Hospital Reina Sofía. Córdoba, Spain

Summary: With the aim of evaluating tolerance to new shorter initiation schedules in subcutaneous immunotherapy everyday clinical practice, a study was carried out using Pangramin Plus® with initiation periods between 3 (Cluster) and 6 (Plus) weeks.

All the information was processed retrospectively and both systemic (SR) and local (LR) adverse reactions occurring between September 2002 and February 2003 were recorded.

A total of 353 patients (261 Plus and 91 Cluster) were included and 2,886 doses were administered (2,166 in initiation and 720 in maintenance). Of these, 800 were with Grass mix extract, 1,141 Grass mix + *Olea,* 273 *Olea,* 73 *Dermatophagoides* mix *and* 599 *Dermatophagoides pteronyssinus*.

As regards adverse reactions (AR), 2.8% of patients showed SR and 4.8% LR, 1.2% of doses caused some type of reaction (SR and LR in 0.3% and 0.9%, respectively). The initiation schedule, first dose or allergens resulted in no significant differences in the frequency of adverse reactions. The Grass mix extract showed the highest frequency of AR.

Sixty-seven percent of SR and 68% of LR were delayed. 64% of these reactions resolved spontaneously while the rest responded favourably to treatment. Adrenaline was administered on one occasion for immediate asthma. There were no cases of anaphylactic shock, hospitalisation or life-threatening situations.

Pangramin Plus® tolerance, therefore, can be classified as good, similar to conventional schedules, but with the benefits of shorter initiation schedules.

Key words: Subcutaneous immunotherapy, tolerance, short initiation schedule.

Introduction

Immunotherapy with allergen extracts has been used as a treatment for immediate or type I hypersensitivity diseases mediated by IgE antibodies (rhinoconjunctivitis, asthma, and severe reactions to insect stings) since it was introduced by Noon [1] and Freeman [2] in 1911. It is currently the only etiological treatment which has proven effective for allergic diseases [3].

Initially, allergen extracts were measured in weight/volume units and in nitrogen protein units. By the 1980s, biological standardization [4] commenced and later, quantification in mass units [5] was developed. As a result, allergen doses were established as μg of active ingredient, leading to safer and more effective immunotherapy.

The standard schedule in the initiation period of subcutaneous immunotherapy involves an increasing weekly dose over a period of 12 to 16 consecutive weeks depending on the manufacturer. However, in recent years, there has been a growing interest in the use of shorter initiation schedules [6], which facilitate immunotherapy compliance and acceptance.

A reduction in the initial period during which the dose is increased results in a number of advantages not

only for patients but also for clinics where this type of treatment is carried out. First of all, there is a reduction in both the number of visits and injections. Second, immunotherapy can start nearer the pollen season in cases of seasonal allergens.

With these benefits in mind, the ALK-ABELLÓ group, in co-operation with numerous clinical groups, has carried out different multicentre studies over the last few years [7-9] administering short schedules which allowed the maintenance dose to be reached in 3 weeks (4 visits, 8 injections). With the same objective, another study[10] was carried out in which the maintenance dose was reached in 6 weeks after 7 weekly doses as opposed to the 13 in the conventional schedule.

Specific immunotherapy can cause adverse reactions. The frequency and severity of these reactions vary among studies and often the data on tolerability cannot be compared due to the fact that the major allergens of the allergen extracts have not always been quantified and also due to the large variability in the schedules administered [11-14]. In addition, the frequency and severity of systemic reactions may depend on the allergy disease and the patient's degree of sensitivity, and on the allergen in question[15].

In this study we have attempted to evaluate in everyday clinical practice the tolerance to immunotherapy with short initiation schedules and different extracts, which all are standardized and quantified in mass units.

Material and methods

Patients

Male and female patients, pollen and mite sensitised and who had received immunotherapy with Pangramin Plus® between September 2002 and February 2003. Patient selection was performed by 7 specialists randomly chosen from the prescribing medical doctors.

Immunotherapy

Immunotherapy was carried out with Pangramin Plus® (ALK-ABELLÓ, S.A.), which was administered subcutaneously as an injectable solution containing allergen extract adsorbed in an aluminium hydroxide gel. Allergen extracts were standardized in mass units and labelled in Specific Treatment Units (S.T.U.) (100 S.T.U. in vial A and 1,000 S.T.U in vial B).

The content of major allergen(s) depended on the allergen composition: Grass mix (*Dactylis, Festuca, Lolium, Phleum, Poa* and *Secale* contained 2.5 µg of Group 5 in the maximum concentration vial), Grass mix + *Olea* (1.25 µg of Group 5 and 7.5 µg of Ole e 1), *Olea europaea* 100% (15 µg of Ole e 1), *Dermatophagoides pteronyssinus* 100% (4 µg Der p 1 and 2 µg of Der p 2) and *Dermatophagoides* mix (4 µg Der 1 and 2 µg Der 2).

The treatment consisted of 2 phases: the initiation phase or dose increase up to the maintenance dose or the maximum tolerated dose by the patient, and the maintenance phase or the repeated administration of this last dose.

The initiation treatment contained one A vial and two B vials while the maintenance treatment contained either two or four B vials. There were two schedules recommended by the manufacturer: the Cluster and the Plus schedules (Table 1).

The maintenance dose for Cluster schedule was reached in 3 weeks, administering 2 injections per day in 4 weekly visits. The maintenance schedule for the Plus dose was reached in 6 weeks and began with vial A, increasing the weekly subcutaneous dose of vial B up to 0.8 mL.

In both types of schedule, 0.8 ml of vial B was then given after 15 days and repeated every four weeks.

Design

Seven allergists were randomly chosen from the prescribing medical doctors. Each patient's initiation schedule (Cluster or Plus) and adverse reactions occurring from September 2002 to February 2003 were retrospectively recorded on a specific form.

The only patients to be considered for data analysis were those whose treatment had been administered in the period defined previously and who were either supervised directly or closely followed by the specialist even when treatment was at an outpatient department or health centre.

Forms

A form was completed for each reaction.

The information to be registered included patient details (initials, age and clinical diagnosis), immunotherapy data (initiation schedule, composition, immunotherapy start date, treatment phase and dose which led to a reaction), data on adverse reactions (dose, description and causal relationship between AR and immunotherapy) as well as reaction outcome (adverse reaction treatment and resolution and the situation regarding immunotherapy following an adverse reaction).

Opinion questionnaire

The clinics who had participated in the study also provided information from a questionnaire about tolerance to shorter initiation schedules. The aim was to obtain the opinion of specialists, based on their experience in clinical practice, regarding tolerance to Pangramin Plus® schedules in comparison with conventional schedules and the advantages that they felt the former offered for compliance with treatment.

Table 1. Initiation Schedules.

	Vial	Week									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**
Cluster	A	0.1+0.2	0.4+0.6								
	B			0.1+0.2	0.4+0.4	0.8	0.8				
Plus	A	0.2	0.4	0.8							
	B				0.1	0.2	0.4	0.8	0.8	0.8	0.8

Table 2. Patients as a function of the immunotherapy composition and initiation schedule.

	Vital status		
Composition	**Plus**	**Cluster**	**Total**
Grass mix	81	9	90
Grass mix + *Olea*	111	28	139
Olea	30	1	31
Dermatophagoides mix	8	–	8
D. pteronyssinus	31	53	85
Total	261	91	353*

* Unknown Schedule for one patient.

Statistical analysis

Statistical analysis was performed with SPSS v11.5 (SPSS Inc. Chicago). The comparison of frequencies was performed by the bilateral Fisher test. P values below 0.05 were considered significant.

Results

Patients

A total of 353 patients were included in the study of which 91 and 261 followed a Cluster and Plus schedule, respectively. The majority of patients received immunotherapy treatment with Grass mix + *Olea*. In Table 2 there is a detailed summary of patients as a function of the type of immunotherapy and initiation schedule.

Immunotherapy

Table 3 shows the number of doses per initiation schedule and immunotherapy phase. 2,886 doses were administered, 2,166 during initiation and 720 during

Table 3. Number of administered doses per allergen extract.

	Initiation		Maintenance		Total
Composition	**Plus**	**Cluster**	**Plus**	**Cluster**	
Grass mix	560	36	186	18	800
Grass mix + *Olea*	763	108	211	59	1.141
Olea	210	4	57	2	273
Dermatophagoides mix	56	–	17	–	73
D. pteronyssinus	217	212	55	112	599*
Total	1.806	360	526	191	2.886*

* Unknown Schedule for 3 doses.

maintenance as well as outlines doses administered per allergen extract. Grass mix + *Olea* made up the largest number of doses.

Tolerance

During the study, 27 patients (7.6% of the total) experienced adverse reactions, patients treated with Grass mix accounting for the majority of these (Table 4).

Twenty eight local reactions were observed (0.9% of doses) and 10 systemic reactions (0.3%). A total of

Table 4. Frequency of adverse reactions per patient and extract.

Composition	Frequency AR
Grass mix	15%
Grass mix + *Olea*	6.4%
Olea	6.4%
Dermatophagoides mix	12.5%
D. pteronyssinus	1%

Table 5. Number and frequency of adverse reactions per initiation schedule and immunotherapy phase.

	Initiation		Maintenance	
	Plus	Cluster	Plus	Cluster
Systemic reactions*	8 (0.44%)	2 (0.55%)	0	0
Local reactions*	27 (1.49%)	0	1 (0.19%)	0

* 3 reactions were SR + LR

Table 6. Number and frequency of AR as a function of doses of extract.

	Systemic reactions	Local reactions	Total
Grass mix*	4(0.5%)	20(2.5%)	22(2.75%)
Grass mix + *Olea***	4 (0.35%)	6 (0.52)	9 (0.78%)
Olea	1 (0.36%)	1 (0.36%)	2 (0.73%)
Dermatophagoides mix	0	1 (1.36%)	1 (1.36%)
Dermatophagoides pteronyssinus	1 (0.16%)	0	1 (0.16%)

* twice were SR+LR
** once was SR + LR

Table 7. Nature of Systemic reactions and onset.

	Immediate (≤ 30 minutes)	Delayed (> 30 minutes)
Grass mix	• Asthma + urticaria + cough • Urticaria + angioedema + cough	• Urticaria • Asthma + rhinitis + conjunctivitis
Grass mix + *Olea*		• Urticaria + angioedema • Rhinitis + urticaria • Urticaria • Asthma + urticaria
Olea	• Conjunctivitis*	
Dermatophagoides pteronyssinus	• Asthma	

* Unknown onset

35 doses resulted in some form of reaction (1.2%) 34 of which occurred during initiation and 1 during maintenance.

As regards administration schedules, only two adverse reactions occurred in the Cluster schedule, both of which were systemic, while the remaining 33 were in the Plus schedule. However, no significant statistical difference was observed between either type of initiation schedule (p=0.67) (Table 5).

Table 6 shows the percentage of both systemic and local adverse reactions as a function of the doses of each extract administered. Grass mix registered the largest percentage of not only systemic but also local reactions.

Delayed reactions and cutaneous symptomatology were the most frequent of systemic reactions (Table 7).

Thirty percent of SR received no treatment, the reaction resolving spontaneously. Only on one occasion (10% of SR), was adrenaline given, together with antihistamines, $ß_2$ agonists and corticoids, for immediate asthma. Treatment with antihistamines associated with a $ß_2$ agonist and corticoids was administered in 20% of SR, antihistamines and corticoids in 20% and antihistamines exclusively in 20%.

None of the doses causing adverse reactions seemed to produce a greater number of reactions.

The schedule was modified 25 times (0.86% of doses). Of these, doses had to be repeated in 12 cases (twice due to a SR, once because of a LR associated with SR and the rest following LR). It was decided that the dose be reduced on 13 occasions (4, 2 and the remaining 7 due to SR, LR associated with SR and LR, respectively). It was not necessary to modify the schedule in one case of LR and one of SR. Information is not available on 9 doses with LR.

None of the adverse reactions required hospitalisation nor did they threaten the patient's life. On 3 occasions patients went to emergency, two because of a SR and one due to LR. Only on one occasion was immunotherapy stopped as a result of an isolated case of LR.

Opinion Questionnaire

The questionnaire was returned by 6 of the 7 clinics. There was a consensus of opinion regarding the advantages of this product as all 6 indicated that it was more convenient for patients and that immunotherapy was more readily-accepted by them as a result. According to these doctors, the patients were also more compliant with the treatment.

Discussion

The aim of this study was to evaluate tolerability to two Pangramin Plus®, shorter- than-conventional, initiation schedules (Cluster and Plus), with different existing allergen extracts.

In order to evaluate tolerance adequately, it is essential to compare data published by other authors who have used identical extracts in terms of standardization both in conventional and short schedules.

The same allergen extract, but following a conventional schedule and using retrospective data, has been used in 3 clinical studies [16-18]. In the first, which took place in an immunotherapy unit, 226 patients received 5,120 doses and the percentage of systemic adverse reactions per dose was 0.29%. In the second study, 88 patients received 1,244 doses and the percentage was 0.32%. Finally, in a more recent multicentre study of 488 patients, the percentage of systemic adverse reactions was similar: 0.3% of the 17,526 doses.

In two studies[19, 7] in which a cluster schedule was followed and the same quality of extracts as ours was used, the percentage of systemic adverse reactions was 0.3% and 1.2% of doses, while in another publication[10], which also referred to a prospective study using a schedule similar to that of the Plus schedule, the percentage was 0.5%.

As such, the 0.3% of systemic reaction per dose in our study is similar to these figures. However, the percentage of systemic reactions per patient was 2.8%, lower than the results obtained in other studies [10, 9, 19] using cluster or plus schedules.

None of the systemic reactions which have been observed during clinical practice over this study period should by any means be considered serious under the existing definition given [20].

Adrenaline was only administered once (associated with corticoids, antihistamines and $ß_2$ agonists) to deal with cough and wheezing which occurred immediately after the administration of a second dose of vial B in the cluster schedule and as a result of which the patient attended emergency. Following the prescribed treatment, the symptoms disappeared in one hour.

Another patient attended emergency because of a delayed SR, having experienced underarm itching, wheals on body and arms, dysphagia and wheezing 4 hours after treatment. These symptoms disappeared after administering corticoids and antihistamines without using adrenalin.

None of the patients who experienced systemic reactions stopped immunotherapy.

The percentage of LR per dosage obtained in this study (0.9%) is somewhat higher than that of others which have followed a conventional schedule [17,18] although lower than those which followed a cluster schedule [9, 19]. In any case, up to 75% of LRs resolved spontaneously.

There was one case of delayed LR where the patient went to emergency and immunotherapy was stopped. A preseasonal schedule had been prescribed, and the reaction took place in February at the third monthly dosage of 0.8 mL of vial B, therefore it was decided to stop immunotherapy.

We have found no differences in tolerance due to vial, dosage, schedule or extract administered.

Grass mix extract had the highest percentage of both systemic and local reactions per dosage which cannot be explained by coseasonality since they occurred in October, November, January and February, mainly in Vitoria, where the allergen pressure is low during these months.

Therefore, an explanation for the greater number of reactions from Grass mix must be due to other factors which still need clarification although this tendency may well indicate that this type of schedule may not be suitable for all allergen extracts. Nevertheless, this result coincides with other studies[21-24] the Grass mix extract being the worst tolerated in both conventional and cluster schedules.

As can be seen from the opinion questionnaire, specialists consider that shorter schedules are more convenient for patients and make immunotherapy more acceptable. Several previous studies [7, 19] have confirmed that a reduction in the number of visits for immunotherapy treatment is an important advantage. Moreover, the financial savings generated by a reduction in the number of visits must also be considered.

In conclusion, the short initiation immunotherapy schedules offer an acceptable tolerance compared to conventional schedules and also a number of advantages, making immunotherapy administration more convenient for both patients and doctors.

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Begoña Gandarias

ALK-ABELLÓ, S.A.
Medical Department
Miguel Fleta, 19
28037 Madrid
Tel.: +34 91 327 61 27
Fax: +34 91 327 61 28
E-mail: begona.gandarias@es.alk-abello.com