Original Article

Prospective safety study of immunotherapy administered in a cluster schedule

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Summary. Cluster immunotherapy is becoming an alternative to conventional IT due to its shorter schedule, but the safety of such schedule is still controversial. At present, only few studies assess the risk of immunotherapy in a prospective manner, in well-controlled patients, using the same extract and intending to evaluate a single schedule. The aim of the present study is to evaluate the safety of a cluster immunotherapy administration regimen.
A total of 91 outpatients (41 male and 50 female), with a mean age of 25 years old (range: 16-50) were included. Sixty-one patients were diagnosed mild to moderate asthma and 30 rhinoconjunctivitis. Forty-six of the enrolled patients were sensitised to pollen (*Lolium perenne* and/or *Olea europea*), 38 to *Dermatophagoides pteronyssinus* and 7 to *Alternaria alternata*. Patients received specific immunotherapy following a five-week cluster schedule. It was considered as a preseasonal treatment, that is, it was accomplished before olive and grass initial pollinating months in this area (March-April). A total 1029 injections were administered during the induction phase. Adverse reactions were assessed and classified according to the EAACI criteria.
The average number of visits to maximum dose was 6 (range 2-10), and 70 patients (77%) reached the maximum between 5-7 visits. In each of the visits an average of 2 (range 1-3) injections were administered. Eighty-one of the 91 initially enrolled patients (89%) completed the cluster schedule.
The total number of reactions were 47 (24 local and 23 systemic). No fatal reactions were observed. Since the total number of administered injections was 1029, the relative frequency of adverse reactions was 4.6% (2.3% local and 2.2% systemic). The percentage of patients affected by systemic reaction was 18% and by local reaction 14%. No relationship can be shown between adverse reactions and gender or disease. However, a clear relationship with the composition of immunotherapy has been shown, with a lower risk of adverse reactions associated with the extract of *D. pteronyssinus*.
The shorter period required to achieve the maintenance dose, with a similar frequency of adverse events, leads to the conclusion that the proposed administration regimen can be an alternative to conventional schedule to increase patient compliance.

Key words:

General	*MeSH*
Allergy	Respiratory Hypersensitivity / Asthma, Rhinitis
Immunotherapy	Desensitisation, Immunologic
Cluster immunotherapy	Drug Administration Schedule
Adverse reaction	Desensitisation, Immunologic / Adverse effects

Introduction

The efficacy of specific immunotherapy (IT) has been recently shown by several well-documented reviews [1-3]. However, the most important drawbacks for their therapeutic use are the difficulties of administration and the adverse events, resulting in low compliance and therefore a lower therapeutic success. In fact, IT administered following a conventional schedule requires a high number of injections along a period of at least 2-5 years, and more specifically, the induction period consists in a once-weekly injection, usually achieving the maintenance dose at 5-6 months. In addition, to decrease the number and severity of adverse events, the injections must be administered at a specifically trained Immunotherapy Unit, under supervision of specialised personnel [4].

Over the last years, some facts as the increasing quality of allergenic extracts, the improvement of standardisation methods and the insight on the triggering mechanisms, have contributed to diminish the number and significance of adverse reactions. However, although the number and importance of adverse events is decreasing, it is still the highest concern with IT. Noteworthy is also the finding that the incidence of adverse events might vary with the use of different extracts or administration regimens.

Different attempts have been made to facilitate the compliance with IT, mainly shorter schedules of administration or new routes of administration still not well established. In this sense, cluster IT is becoming an alternative to conventional IT due to its shorter schedule. On the other hand, the safety of cluster versus conventional schedule is still controversial: Although the use of shorter schedules is crucial to reduce the risk of life-threatening conditions in the case of sensitivity to Hymenoptera, more justification is needed to evaluate the cost/benefit ratio in other allergic diseases caused by common allergens.

At present, only a few studies assess the risk of immunotherapy in a prospective manner, in well-controlled patients, using the same extract and intending to evaluate a single schedule. The aim of the present study is to evaluate the safety of a cluster immunotherapy schedule in a group of patients with allergic respiratory disease sensitised to common allergens.

Material and methods

Design

This is a prospective, open label study, carried-out in an Immunotherapy Unit, located at the Department of Allergology of a General Hospital. Study was performed after being approved by the ad hoc committee and specific informed consent was obtained from the patients prior to the administration of therapy.

Patients

A total of 91 out-patients (41 male and 50 female), with a mean age of 25 years-old (range: 16-50) were included.

The diagnosis of allergic disease was performed through a detailed clinical history (including allergen exposition and risk factors), physical examination, positive skin prick test and clinical laboratory tests. Additionally, lung function was assessed by spirometry. Sixty-one patients were diagnosed mild to moderate asthma and 30 rhinoconjunctivitis.

Allergen determination was performed by skin prick test (Prick Test Diagnóstico, Bial-Arístegui, Spain) and specific IgE determination. Skin-prick test panels included pollen (*Lolium perenne, Cynodon dactylon, Secale cereale, Parietaria officinalis, Artemisia vulgaris, Chenopodium album*), mites (*Dermatophagoides pteronyssinus, D.farinae*), mould (*Alternaria alternata*) and epithelia (dog, cat). Forty-six patients were sensitised to pollen (*Lolium perenne,* (LOL) and/or *Olea europea* (OLE)), 38 to mites (*Dermatophagoides pteronyssinus*, (DPT)) and 7 to mould (*Alternaria alternata*, (ALT)).

All the patients met the criteria for specific immunotherapy, according with the official position papers [4], and so were eligible for the treatment. Patients with a previous desensitisation treatment or presenting sensitisation to other than the previously mentioned allergens, pregnancy, or other contraindications for IT, were excluded. Whenever possible, allergen avoidance was recommended, and, when necessary, symptoms were also controlled by pharmacological treatment.

Immunotherapy

All the patients received specific immunotherapy provided by the same manufacturer (Allergovac Depot®, Bial-Arístegui, Spain). The product consists of 4 vials (labelled #0 to #3) of 10-fold dilutions in a matrix of 0.33% aluminium hydroxide. The highest concentrations (Vial #3) of the used allergens were established by a biological standardisation program according to the EAACI recommendations [5], resulting as follows: OLE, 194 UBE/ml; LOL 2,830 UBE/ml; OLE+LOL, 1,512 UBE/ml; DPT, 860 UBE/ml; ALT, 1,672 UBE/ml. Standardisation procedure was based on RAST inhibition in comparison to an in-house reference preparation [6]. In brief, an allergenic extract was obtained from each raw material, kept in freeze-dried aliquots, labelled as IHR and evaluated in its biologic activity by skin test end-point titration in a sample population of at least 20 patients allergic to each inhalant. Skin test was carried out in duplicate with four three-fold concentrations of allergenic extracts. Wheal areas were recorded after 20 min., transferred to a translucent tape, and later measured by digitalisation by means of

Table 1. Classification of patients according to diagnosis and composition of immunotherapy.

COMPOSITION IT	DIAGNOSIS		TOTAL
	Asthma	Rhinitis	
OLE 100%	1	2	3
LOL 100%	5	3	8
LOL50%+OLE50%	26	9	35
DPT100%	23	15	38
ALT100%	6	1	7
TOTAL OF PATIENTS	61	30	91

computer-assisted design software. The dose response curve was obtained by plotting the mean wheal areas elicited by each allergen concentration (semi-logarithmic mode). An SPT value (in mg/ml) was interpolated and defined as the extract concentration eliciting a wheal area the geometric mean of which was equal to that produced by the histamine reference in the same population. In our system, this figure is arbitrarily multiplied by 10,000 to obtain the unitage of biological activity of the IHR, i.e. UBE/ml (Equivalent Biological Units per millilitre), which is used to label the products equilibrated with respect to the internal reference.

The number of patients receiving immunotherapy, according to the diagnosis and the composition of allergenic extracts of administered immunotherapy, are shown in Table 1.

Immunotherapy was administered during the induction phase according to a cluster schedule as detailed in Table 2. Injections were alternately given in each arm. The treatment was always administered by the same trained allergologist, who eva-luated possible modifications: the schedule was modified, according to the recommen-dations of WHO/EAACI, when any grade 2-3 adverse reaction occurred or it was suspended when a grade 4 reaction appeared, as well as under the usual general conditions (exacerbation of disease, presence of infections, etc.). In the case of severe systemic reaction or large repeated local reaction, the patient was transferred to a conventional schedule. No pre-medication was given. It was considered as a preseasonal treatment, that is, it was accomplished before olive and grass initial pollinating months in this area (March-April).

Once the maximum dose was reached, maintenance therapy with the same concentration was administered at the corresponding outpatient clinic, every month for a total period of treatment of at least 2 years. No adverse reactions were recorded during the maintenance period.

Table 2. Cluster schedule of immunotherapy.

DAY	VISIT	VIAL	VOLUME (ml)	INTERVALS
1	1	1	0.2	30 min
			0.4	30 min
			0.8	30-45 min. under observation
7	2	2	0.2	30 min
			0.4	30 min
			0.8	30-45 min. under observation
14	3	3	0.1	30 min
			0.2	30-45 min under observation
21	4	3	0.4	30 min
			0.4	30-45 min under observation
28	5	3	0.4+0.4*	30-45 min under observation
35	6	3	0.5+0.5*	30-45 min under observation

*Given consecutively in each arm.

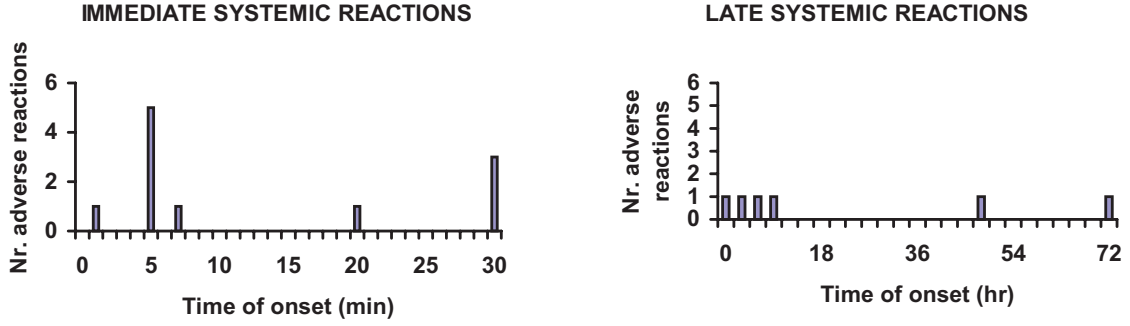

Figure 1. Time of occurrence of adverse reactions.

Table 3. Characteristics of adverse reactions.

Patient nr.	Type of reaction	Symptoms	Time of reaction	Treatment						Dropped out
				Cold	AntiH1	Beta2	Cortic.	Epin.	Hospit.	
1	Local	Wheal>10cm	24 h	N	Y (p.o.)	N	N	N	N	N
	Local	Wheal>10cm	24 h	N	Y (p.o.)	N	N	N	N	
	Local	Wheal>10cm	24 h	N	Y (p.o.)	N	N	N	N	
2	Local	Wheal>5 cm	30 m	N	Y (p.o.)	N	N	N	N	N
	Local	Wheal>10cm	24 h	N	Y (p.o.)	N	N	N	N	
11	Systemic	RC	48 h	N	Y (p.o.)	N	N	N	N	N
12	Local	Wheal>10cm	24 h	N	N	N	N	N	N	N
14	Systemic	Urticaria	72 h	N	Y (p.o.)	N	N	N	N	N
16	Systemic	Urticaria+BC	3 h	N	Y (p.o.)	N	Y (p.o.)	N	N	N
19	Local	Wheal>8cm	24 h	N	Y (p.o.)	N	N	N	N	N
20	Systemic	RC	5 m	N	Y (p.o.)	N	N	N	N	N
23	Systemic	BC	20 m	N	N	Y	Y	N	N	N
24	Systemic	Urticaria	75 m	N	Y (i.m.)	N	Y (i.m.)	Y	N	N
	Systemic	Urticaria	5 m	N	Y (i.m.)	N	Y (i.m.)	Y	N	
	Local	Wheal>5cm	5 m	N	Y	N	N	N	N	
28	Local	Wheal>5cm	30 m	Y	N	N	N	N	N	N
	Local	Wheal=8cm	24 h	N	Y (p.o.)	N	Y (top.)	N	N	
	Local	Wheal=8cm	24 h	N	Y (p.o.)	N	Y (top.)	N	N	
29	Systemic	BC	30 m	N	N	N	N	N	N	AR
	Systemic	RC+BC	1 m	N	Y (p.o.)	Y	Y (p.o.)	Y	N	
30	Systemic	Inespecific	30 m	N	N	Y	N	N	N	N
39	Local	Wheal=8cm	6 h	Y	Y (p.o.)	N	N	N	N	Compl.
	Local	Wheal=5cm	30 m	Y	Y (p.o.)	N	N	N	N	
40	Systemic	Anaphylaxis	30 m	N	Y (p.o.)	Y	Y (p.o.)	Y	N	AR
	Local	Wheal=6cm	30 m	N	Y (p.o.)	N	N	N	N	
47	Local	Wheal=5cm	30 m	Y	Y (p.o.)	N	N	N	N	N
	Local	Wheal=5cm	30 m	Y	Y (p.o.)	N	N	N	N	
	Local	Wheal=10cm	48 h	N	Y (p.o.)	N	Y (top.)	N	N	
	Local	Wheal=10cm	48 h	Y	Y (p.o.)	N	Y (top.)	N	N	
49	Local	Wheal=10cm	48 h	N	Y (p.o.)	N	Y (top.)	N	N	N
	Local	Wheal=8cm	48 h	N	Y (p.o.)	N	Y (top.)	N	N	
	Local	Wheal=8cm	48 h	N	Y (p.o.)	N	Y (top.)	N	N	
50	Systemic	Anaphylaxis	5 m	N	Y (p.o.)	Y	Y (p.o.)	Y	N	AR
52	Systemic	RC	5 m	N	Y (p.o.)	N	N	N	N	AR
	Systemic	RC	30 m	N	Y (p.o.)	N	N	N	N	
	Systemic	BC	5 m	N	Y (p.o.)	Y	Y (p.o.)	N	N	
53	Systemic	RC	5 m	N	Y (p.o.)	N	N	N	N	N
55	Systemic	RC	30 m	N	Y (p.o.)	N	N	N	N	N
58	Local	Wheal=10cm	24 h	N	N	N	N	N	N	N
61	Systemic	Urticaria	2 h	N	Y (p.o.)	N	N	N	N	AR
	Systemic	Urticaria	8 h	N	Y (p.o.)	N	N	N	N	
66	Systemic	RC	5 m	N	Y (p.o.)	N	N	N	N	N
	Local	Wheal=5cm	30 m	Y	Y (p.o.)	N	Y (top.)	N	N	
86	Local	Wheal=10cm	24 h	Y	N	N	N	N	N	Compl.
87	Systemic	RC+BC	8 h	N	Y (p.o.)	Y	Y (p.o.)	N	N	AR

Y= Yes; N= No; RC= Rhinoconjunctivitis; BC= Bronchoconstriction; Cortic.= Corticosteroid administered; Epin.= Epinephrine administered; Hospit.= Hospitalisation required; AR= Dropped out by adverse reaction; Compl.= Dropped out by poor compliance.

Assessment of adverse reactions

Before each injection, the patient was re-examined, and a peak flow determination was performed and the treatment was administered only if the clinical situation was the appropriate one. After the injection, the patient remained at the Immunotherapy Unit under medical observation for

30-45 minutes. At the end of this period, the area of injection was examined by the allergologist and a new peak flow determination was performed. During the following visit, the patient was also interviewed to check the presence of any late reaction.

A reaction was classified as immediate when it occurred within 30 minutes of the injection, and it was late when it occurred up to 72 h post-injection. The swelling was considered local reaction if the diameter was larger than 5 cm for immediate reactions or larger than 8 cm in the case of late reaction. The systemic reactions were classified according to the EAACI criteria [4].

The adverse reactions were treated, as necessary, by antihistamine drugs (p.o. or i.m.), nebulised beta-adrenergic agents or corticosteroids (p.o., i.m., or i.v.). All reactions were treated in the clinic and no patient required further hospitalisation.

The time of latency, symptoms and the treatment required for each reaction were also recorded on the patient's case report form.

Statistical methods

The Chi-square test was used to compare the side effects elicited by different conditions (gender, diagnosis, composition). An ANOVA model was designed to evaluate the effect of gender and diagnosis as factors and age as covariate over the number of adverse reactions. Another ANOVA was designed to evaluate the same factors over the number of doses.

Comparison between two groups was performed by the t-Student test. Comparison between more than two groups was performed by the non-parametric Kruskal-Wallis test. The relationship between two continuous variables was performed by the non-parametric r-Spearman test; and between two categorical variables, by the χ^2 test.

The level of significance was set at $p<0.05$.

Results

Immunotherapy

A total 1,029 injections were administered during the induction phase. There were no differences in the number of injections by composition of IT or gender or diagnosis of patients (data not shown).

Eighty-one of the 91 initially enrolled patients (89%) completed the cluster schedule. Immunotherapy was interrupted in 6 patients (7%) due to adverse reactions (1 in the OLE group; 3 in the LOL+OLE group; 2 in the ALT group). Four additional patients (4%) were dropped-out by lack of compliance (1 in the LOL group; 3 in the LOL+OLE group).

The average number of visits to maximum dose was 6 (range 3-10), and 74 patients (91%) reached maintenance dose in a maximum 8 visits. Only 3 patients (3.7%) needed the maximum number of 10 visits. The maintenance phase was then reached in a mean of 5 weeks. An average of 12 injections for patient (range 8-17) were administered.

Most of the patients (76.5%) achieved the predicted maximum dose with 1ml of vial #3, and an additional 18.5% achieved the 0.8 ml of vial #3. For the rest of patients, a lower dose was necessary (0.7, 0.6, 0.5 and 0.2 ml of vial #3, respectively).

Adverse reactions

The characteristics of each adverse reaction, including the administered treatment, are summarised in Table 3. The total number of reactions were 47 (24 local and 23 systemic). No fatal reactions were observed. Since the total number of administered injections was 1029, the relative frequency of adverse reactions was 4.6% (2.3% local and 2.2% systemic). The reactions were also classified according to the time of occurrence as immediate (within 30 minutes after

Table 4. Nr. of adverse reactions, classified by patient's gender and by disease.

		Nr. patients	Nr. AR	Nr. LIR	Nr. LLR	Nr. SIR	Nr. SLR
Gender	Male	41	18	2	6	5	5
	Female	50	29	6	10	9	4
Disease	Asthma	61	32	5	15	9	3*
	Rhinitis	30	15	3	1	5	6*
Total		91	47	8	16	14	9

AR: Adverse reactions. LIR: Local Immediate Reaction. LLR: Local Late Reaction. SIR: Systemic Immediate Reaction. SLR: Systemic Late Reaction.
* $p<0.05$

Table 5. Nr. of patients affected by adverse reactions, classified by gender and by disease.

		Nr patients TOTAL	Nr. patients with AR	Nr. patients with LIR	Nr. patients with LLR	Nr. patients with SIR	Nr. patients with SLR
Gender	Male	41	11	6	4	5	3
	Female	50	15	7	6	6	3
Disease	Asthma	61	17	10	9	7	1*
	Rhinitis	30	9	3	1	4	5*
Total		91	26	13	10	11	6

AR: Adverse reactions. LIR: Local Immediate Reaction. LLR: Local Late Reaction. SIR: Systemic Immediate Reaction. SLR: Systemic Late Reaction.
* p<0.05

Table 6. Nr. of adverse reactions, classified by composition of immunotherapy.

		Nr patients TOTAL	Nr. patients with AR(%)	Nr. patients with LIR(%)	Nr. patients with LLR(%)	Nr. patients with SIR(%)	Nr. patients with SLR(%)
Extract	Pollen	46	20 (43.5)	12 (26.1)	9 (19.6)	7 (15.2)	5 (10.9)
	DPT	38	1 (2.6)	0	0	0	1 (2.6)
	Alternaria	7	5 (71.4)	1 (14.3)	1 (14.3)	4 (57.1)	0
Signif.		91	p<0.001	p<0.01	p<0.05	p<0.001	NS

AR: Adverse reactions. LIR: Local Immediate Reaction. LLR: Local Late Reaction. SIR: Systemic Immediate Reaction. SLR: Systemic Late Reaction.

injection) or late reaction (up to 72 h after injection), resulting 25 and 22 reactions respectively (Fig. 1).

No relationship was shown between the number of adverse reactions and age, gender or disease of patients, except for systemic late reactions, where a higher frequency was recorded in the case of patients affected by rhinitis (Table 4).

The analysis was also performed by the number of patients affected. A total 26 patients (29%) suffered from adverse reactions (14 of them only one reaction, 6 of them 2 reactions, another 5 patients with 3 reactions and one patient suffered from 4 reactions). Among them, 13 (14%) suffered systemic reaction, 10 (11%) local reaction and 3 (3%) both systemic and local reaction (Systemic reaction: 18%; Local reaction: 14%). No relationship was shown between the incidence of adverse reactions and age, gender or disease of patients, except for SLR, where a higher incidence is shown for patients with rhinitis (Table 5).

The influence of allergen composition was also evaluated. The adverse reactions to DPT were significantly lower than in the other two groups evaluated (Table 6).

Discussion

Once the efficacy of specific immunotherapy has been clearly established, there is a long way to improve the comfort and compliance of the treatment. Many studies have shown that compliance increases by decreasing complexity of immunotherapy [7]. Diminishing the time required to reach the maintenance dose through the use of a cluster schedule saves time and might increase the compliance with the treatment or the initiation of immunotherapy in patients otherwise in pharmacological control.

Cluster schedule is a method for advancing an allergic patient to the maintenance dose in a shorter period of time. Although some authors have even proposed a one-day schedule, such a dramatic schedule might associate an increased risk of adverse events, mainly systemic reactions [7]. In fact, the regimen proposed here was designed to achieve the maintenance period in a total 6 visits and that schedule was complied by the majority of the patients. Even though some patients (3.3%) required the maximum number of 10 visits, this is far lower than the usually required in a conventional programme. Thus, the time to reach the maintenance dose under cluster immunotherapy (5 weeks) is half the time reported by other authors under conventional regimen (13 weeks) [8].

Although some authors have reported that shorter schedules are less advantageous than the conventional schedule because the former have more adverse events with similar efficacy [9], those results can be controversial because they arise from a analysis of efficacy and not from an "intention to treat" analysis. In

addition, the frequency and severity of the adverse events shown in the present study do not significantly differ from those usually reported for conventional immunotherapy. Moreover, results arising from others in our geographical area show that 96% of patients on conventional IT reached the recommended dose, data not significantly different from the 89% of the present study. The high compliance achieved with the proposed schedule is also remarkable, since only 4 patients were dropped out due to poor compliance. This lack of compliance does not seem to be related to the incidence or severity of adverse events, since 2 of the 4 dropped out patients did not have any reaction. Moreover, in the present study all the severe reactions (two episodes of anaphylaxis) occurred within the period of 30 min. surveillance and the reactions after this period were less severe.

The risk of side effects of immunotherapy might vary because of manufacturer differences in allergen standardisation and potency [10] or with the employment of aqueous or depot extracts [11]. To avoid variations due to the use of extracts of different origin or different type, all the patients received the same commercial preparation.

Hypothetically, it can also rely in some patient characteristics, such as gender, age or disease, but we have not found any relationship either by the analysis of the number of affected patients or by the analysis of the number of reactions. Although some authors have seen differences in the frequency and severity of adverse effects depending on the disease [8], we could only show a statistically significant difference in the incidence of Systemic Late Reactions, being 10-fold higher in patients affected by rhinitis than in patients suffering from asthma, consistent when analysed by number of adverse reactions and by number of affected patients. However, the authors do not exclude the possibility that this finding could be considered as an artifact due to the low number of SLR recorded, and deserves further investigation.

The influence of immunotherapy composition on the number of adverse reactions has been clearly established, even using extracts of similar type, from the same manufacturer and the same dose schedule [12].

Finally, the incidence of adverse events of immunotherapy might also vary with the use of different schedules. With regard to the incidence of adverse events, our results are in agreement with other authors using similar cluster schedules [12].

In a similar study, Tabar et al. [8] showed a lower prevalence of local and systemic reactions (10.5 and 4.8% of patients, respectively) with a conventional and perennial schedule. In addition, 3.1% of the patients could not reach the recommended maximum dose, versus 9.1% in this study. However, the most surprising finding is that in the study of Tabar et al. the group of patients sensitised to *D. pteronyssinus*, presented the higher risk of systemic reactions, just the opposite of what our results show.

In a large review and retrospective study, Luigi et al. [13] showed that systemic reactions may range from 0 to 55.6% of patients with accelerated schedules and from 0 to 46.7% of patients with conventional schedules, that is with very few differences among them. Their own results with a conventional schedule showed even lower rates of incidence, around 2% of systemic reactions during the induction phase. The influence of allergen causing the reactions is similar to our results, except in the case of *Alternaria* with a very low percentage of systemic reactions, probably due to the low number of patients treated with this allergen.

As mentioned above, the opposing results between authors in the percentage of affected patients and furthermore, the differential influence of composition on the incidence of adverse events may rely on the differences between commercial preparations. In a study using the same therapeutic schedule in patients of the same geographical area Gastaminza et al. [10], have shown a dramatic difference in the number of adverse reactions, and more specifically late adverse reactions, according to the commercial extract.

Noteworthy is the finding arisen from the review of literature, that very few life-threatening reactions have been reported in the entirety of references included in the present paper.

In conclusion, the results arising from a robust, prospective study, to evaluate the possible risk benefit ratio of a cluster schedule are presented here. The shorter period required to achieve the maintenance dose, with a similar frequency of adverse events, leads to the conclusion that the proposed administration regimen can be an alternative to conventional schedule to increase patient compliance. Therefore, it can not be excluded that results presented here might slightly change with the use of other extracts or other preparations.

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