A. Nieto García[1], S. Nevot Falcó[2], T. Carrillo Díaz[3], J.Á. Cumplido Bonny[4], J.P. Izquierdo Calderón[5], J. Hernández-Peña[6]

Safety of cluster specific immunotherapy with a modified high-dose house dust mite extract

[1]*Pediatric Allergy Unit. University Hospital La Fe. Valencia. Spain.*
[2]*Allergy Unit. Althaia foundation. San Joan de Déu Hospital. Manresa. Spain.*
[3]*Allergy Unit. University Hospital Dr. Negrín. Las Palmas de Gran Canaria. Spain.*
[4]*Allergy Unit. University Hospital Dr. Negrín. Las Palmas de Gran Canaria. Spain.*
[5]*Medical Department, Merck, S.L., Spain.*
[6]*Allergy Division, Merck, S.L., Spain* - E-mail: jenaro.hernandez@merckgroup.com

Key words

Subcutaneous immunotherapy (SCIT); dust mites; high-dose allergoid cluster schedules; safety

Corresponding author
Jenaro Hernández-Peña.
María de Molina, 40. 28006. Madrid. Spain
Phone: +34917455624
Fax: +34917454444
E-mail: jenaro.hernandez@merckgroup.com

Summary

Introduction. *Although the efficacy and safety of high dose hypoallergenic mite subcutaneous immunotherapy (SCIT) using a conventional administration schedule has already been demonstrated, there is no reported experience on the safety of these extracts with cluster schedules. We wanted to determine whether the use of a cluster schedule of a hypoallergenic allergen with a high concentration of house dust mite allergens commonly used in normal practice was safe and well-tolerated in patients with dust mite allergy.* ***Material and Methods.*** *Multicentre, observational, retrospective study of dust mite allergic patients treated with a cluster schedule of SCIT (Acaroid®; Day 1: 300/300 therapeutic units, TU – Day 8: 1000/1000 TU- Day 15: 3000/3000 TU) in 23 Spanish sites.* ***Results.*** *Cluster schedule was used on 434 patients (40.1% children), with a total of 3256 doses (38.2% in children). There were 88 clinically relevant adverse reactions, 79 out of them local and 9 systemic (but mild-moderate) that amounted to 2.7% of all the administered doses. All the patients fulfilled the cluster schedule.* ***Conclusions.*** *Cluster schedule with high dose hypoallergenic mite-SCIT was safe and well-tolerated in routine clinical practice. Therefore, its use could reduce the costs and time needed to achieve the desired maintenance dose and increase compliance.*

Introduction

Allergen immunotherapy consists of the administration of increasingly larger doses of an allergen extract up to the optimal maintenance dose to an allergic patient so as to induce immunologic tolerance and to improve the symptomatology that appears when exposed to the causal allergen.

The efficacy of specific immunotherapy to treat allergies has been clearly demonstrated. Regarding subcutaneous immunotherapy (SCIT) different meta-analyses back its efficacy in bronchial asthma and in allergic rhinitis (1-5).

Cluster SCIT is a variation of conventional SCIT. The build-up phase up to a therapeutic maintenance dose is much shorter with cluster than with conventional SCIT. As a consequence, patients generally achieve the benefits of immunotherapy much faster, what, at the same time, improves compliance.

Cluster SCIT involves giving two or more series of allergy injections at each visit, usually separated apart by 20 to 30 minutes. This procedure is performed once a week, and allows for a person to get to their maintenance dose much faster than with the traditional immunotherapy that can last up to 20 weeks. One study of 239 patients with house dust mites allergy designed to compare the safety and efficacy of a cluster and a conventional schedule with the same therapeutic extract found no difference between any of them in terms of adverse reactions (6). Cluster schedules reduce of-

fice visits, safe patients' time and benefits of immunotherapy can be felt quicker, what improves compliance of a treatment that can last no less than 3 years.

Although different cluster schedules are widely considered as adequate alternatives to conventional allergen SCIT (6, 7), the fact that there is no exact correlation between the techniques used by the different manufacturers and the standardization and quantification of their allergen extracts, makes results obtained regarding safety of these cluster schedules not comparable among them (8).

The efficacy and safety of hypoallergenic therapeutic extracts with a high concentration of house dust mite major allergens (Acaroid®) using a conventional administration schedule has been demonstrated elsewhere (9, 10). However, there is no reported experience on the safety of this preparation when cluster schedules are used, and conclusions obtained from other studies with different therapeutic extracts using a different composition are not comparable. Therefore, the aim of the present study was to determine whether or not the use of a cluster schedule with an allergoid with a high concentration of dust mite modified allergens was a safe and well tolerated option in patients with house dust mite allergy.

Material and methods

Allergen extract composition

The tested product Acaroid® (Allergopharma KG, Reinbek, Germany) is an aluminum hydroxide-adsorbed depot allergoid preparation of standardized (in therapeutic units, TU) high concentrations of powdered diafiltered dust mite allergens modified with formaldehyde and glutaraldehyde. There are two different concentrations, A strength (1,000 TU/mL), and B strength (10,000 TU/mL). The manufacturer recommended maintenance dose is 0.6 mL B strength (6,000 TU). Allergens quantified in the last step prior to allergoidization are 11.66µg/mL Der p 1, and 10µg/mL Der p 2 in the 100% *Dermatophagoides pteronyssinus* formulation, and 20µg/mL Der f 1 and 15µg/mL Der f 2 in the 100% *Dermatophagoides farinae* formulation.

Study design

This was an observational, retrospective and multicentre study carried out in 23 different hospitals in Spain involving 42 investigators, and approved by the ethical review board of the University Hospital La Fe, Valencia.

During the observational period, researchers gathered data from those patients that met inclusion criteria for the study (age 5-65, IgE mediated rhinitis and/or bronchial asthma due to house dust mites) and that, as part of their usual normal practice, were considered to be treated with Acaroid® following a cluster schedule. All the local and systemic adverse reactions related to the administration of the product were reported, as well as the physician's decision of modifying symptomatic treatment.

The indication of immunotherapy was done following the EAACI Immunotherapy Committee Guidelines (11). The systemic adverse reactions were described and graded according to the WAO grading system (12).

When the adverse reactions took place within the first 30 minutes after administration of the product, they were considered as immediate, while they were considered as delayed if they happened after the 30 minutes limit. Local adverse reactions were assessed depending on the diameter of the skin lesion, and considered as clinically significant if larger than 5 cm for immediate reactions, or than 10 cm for delayed reactions (in the event of children, larger than 3 and 7 cm, respectively). Systemic reactions were classified according to the WAO recommendations.

As it was a retrospective study, no specific cluster schedule was mandatory. Rather, only usual daily clinical practice data were recorded.

Statistical analysis

The estimated sample size was calculated bearing in mind the number of participant sites and their potential for recruitment. Since it was an observational retrospective study depending on the feasible number of patients to whom every researcher might consider the cluster administration of Acaroid® as adequate in their usual clinical practice, it was not possible to figure out the optimal sample size upfront.

Feasibility estimations suggested around 13 sites in Spain in which cluster schedules with Acaroid® were normally used, and each of them might enroll between 25 and 40 patients with the specified inclusion criteria. Hence, 400 patients were deemed as a reasonable size. Assuming 2.6% AEs, the detected 95% interval of confidence limits would be 0.5% and 5.6%.

Descriptive analyses of the recorded variables were done. Means and standard deviations were used in the case of normal distributions, and median and interquartilic range for non normal distributions. Proportions were used for cathegorical variables. The relationship between variables

Table 1 - Population demographics and administration schedule details.

Population	Total	Adults	Children
No.	434	260	174
Age			
Range	5 - 65	17 - 65	5 - 16
Mean (SD)	21.4 (12.1)	29.3 (9.6)	1.2 (3.4)
Diagnostic conditions			
Rhinitis	420	231	166
Conjunctivitis	295	156	115
Bronchial asthma	228	122	111
Immunotherapy – Acaroid composition			
D. pteronyssinus 100%	286 (65.9%)	172 (66.1%)	114 (65.5%)
Dermatophagoides Mix	148 (34.1%)	88 (33.8%)	60 (34.5%)
Total number of doses	3256	2011	1245

was studied by means of bivariate associations. The level of statistical significance was set at 0.05%.

Results

Between July and September 2010, data from patients diagnosed with dust mite IgE-mediated rhinitis and/or bronchial asthma treated with a cluster schedule of Acaroid® from September 1st 2009 and May 31st 2010 were recorded. A total of 434 patients aged between 5 and 65, 174 (40.1%) out of them were children were enrolled into the study. A total of 3256 doses (2011 of them to adults and 1245 to children) were given. Table 1 shows demographic data of both populations and Table 2, details of the cluster administration schedule: Acaroid®; Day 1: 300/300 therapeutic units, TU – Day 8: 1000/1000 TU- Day 15: 3000/3000 TU.

Of note, the fact that 111 children (63.7%) and 122 adults (46.9%) were previously diagnosed with bronchial asthma was remarkable (p=0.0008).

Table 2 - Cluster schedule details.

Day	Vial - Strength	Unit dose (mL / TU)	Total dose (TU)
1	A	0.3 / 300	600
	A	0.3 / 300	
8	B	0.1 / 1000	3000
	B	0.2 / 2000	
15	B	0.3 / 3000	6000
	B	0.3 / 3000	

There were 88 reported adverse reactions (2.7% of the total number of administered doses), 79 (2.4%) out of them local and the other 9 (0.3%) systemic (Table 3).

As for local reactions, 50 (1.5% of administered doses) out of them were immediate-onset: 28 (2.2%) in children and 22 (1.1%) in adults. The remaining 29 (0.9%) were delayed-onset reactions: 11 (0.9%) in children and 18 (0.9%) in adults (Table 3). Sixty-six adverse reactions (42 immediate, and 24 delayed onset) were linked to the use of 100% *Dermatophagoides pteronyssinus* extract, and the other 13 (8 immediate and 5 delayed onset) were linked to mixed *Dermatophagoides* extracts.

Twenty-four (48%) episodes out of 50 local immediate reactions did not need any treatment and the remaining 52% episodes were treated with just local application of ice, and the prescription of an oral antihistamine in 6 (12%) cases. Twenty (69%) out of 29 local delayed reactions had no need of treatment; the other 9 (31%) episodes were controlled with local ice and oral antihistamines. There were 3 episodes in which local reactions took place associated to the 0.6 mL B-strength vial and investigators decided to go on with a maintenance dose of 0.5 mL B-strength with no problem.

Regarding the 9 systemic adverse reactions, they affected only 6 patients (1.4%), with 6 (0.2% of total doses) immediate and 3 (0.1% of total doses) delayed-onset reactions, respectively. No differences in terms of composition of the extract were observed, and only one of these reactions happened in a child.

There were 6 immediate systemic adverse reactions in 3 patients. Patient number 56 had a mild rhinitis, 20 minutes after the second dose of 0.3 mL A-strength vial, and

Table 3 - Total adverse reactions and their proportion of doses (%, relative or total).

	Adults (2011 doses)		Children (1245 doses)		Total (3256 doses)
	Immediate	Delayed	Immediate	Delayed	
Local	22 (1.1%)	18 (0.9%)	28 (2.2%)	11 (0.9%)	79 (2.4%)
Systemic	6 (0.3%)	2 (0.1%)	0 (0.0%)	1 (0.1%)	9 (0.3%)
Total	28 (1.4%)	20 (1.0%)	28 (2.2%)	12 (1.0%)	88 (2.7%)

no need of symptomatic treatment. The other 5 adverse reactions were mild asthma, 2 in patient number 311 and 3 in patient number 312, all of them associated to B-strength vial. A single dose of salbutamol was used to control only 2 of them (one for every patient), with no modification of the administration SCIT schedule. Tables 4 and 5 describe these systemic adverse reactions.

The only systemic reaction recorded in a pediatric patient was a delayed urticaria/angioedema episode (96 hours after administration of second day cluster dose) that did not need symptomatic treatment and was even able to tolerate third day cluster dose (0.3mL-0.3mL B-strength vial).

All the remaining 431 patients included in this study completed the cluster SCIT schedule, and achieved the recommended maintenance dose.

Discussion

The aim of this study was to collect data on the safety and tolerance of the use of cluster schedules with Acaroid® taking advantage of the usual daily practice in our country. The specific cluster schedule used only indicates the routine preference of the physicians participating in the

Table 4 - Number and severity of systemic reactions.

	Immediate onset			Delayed onset		
	No.	% patients	% total doses	No.	% patients	% total doses
Grade 1	1	0.2	0.03	0	0.0	0.0
Grade 2	5	0.5	0.15	3	0.7	0.1

Table 5 - Description of systemic reactions.

Patient No.	Age	Gender	Composition of extract*	Diagnosis	WHO Grade	Time of onset
56	35	Female	D.Mix	Rhinitis & asthma	1; rhinitis: 20 minutes	Immediate
74	21	Female	D.Mix	Rhinoconjunctivitis & asthma	1; rhinitis: 720 minutes	Delayed (3 h)
84	6	Male	D.Mix	Rhinoconjunctivitis & asthma	2; cutaneous: 3 days	Delayed (96 h)
311	27	Female	D.Mix	Rhinitis & asthma	2, asthma: 15 minutes	Immediate
311	27	Female	D.Mix	Rhinitis & asthma	2; asthma: 20 minutes	Immediate
312	21	Female	D.pt 100%**	Rhinoconjunctivitis & asthma	2; asthma: 15 minutes	Immediate
312	21	Female	D.pt 100%	Rhinoconjunctivitis & asthma	2; asthma: 20 minutes	Immediate
312	21	Female	D.pt 100%	Rhinoconjunctivitis & asthma	2; asthma: 20 minutes	Immediate
342	24	Female	D.pt 100%	Rhinitis & asthma	2; asthma: 120 minutes	Delayed (2 h)

**D.Mix:Dermatophagoides Mix (D. pteronyssinus and D. farinae) / D.pt 100%: Dermatophagoides pteronyssinus*

study, and under no circumstances was it considered as a prerequisite for the study, nor was it an objective of this study to compare between adult and pediatric subpopulations, despite the fact of the high proportion of children in the sample. The dose of 0.6 mL of the B-strength vial was regarded as the final desired dose to achieve because it is the ideal maintenance dose recommended by the manufacturer.

The assessment of efficacy of Acaroid® in the treatment of dust mite IgE-mediated rhinitis and/or bronchial asthma was never a goal of this study since it has already been demonstrated elsewhere (9, 10), and that was the reason why a double-blind placebo controlled study, serology determination, medication or symptoms scores were not done.

The 434 patients studied, (260 adults and 174 children), along with the fact that all the patients achieved the maintenance dose makes to consider that the sample size was large enough so as to conclude whether cluster SCIT with Acaroid® is safe or not.

The frequency of adverse reactions was in line with other studies in which cluster schedules with a different depot extract were assessed (6, 7). It seems that the incidence of local adverse reactions using a cluster schedule was at least similar to that of conventional administration but at low costs associated to reduction of patient visits for extract administration and a lower demand of health resources, improving patients' compliance to treatment.

In a recently published work by Copenhaver et al (13), the safety profile of a cluster schedule SCIT was analysed retrospectively in 441 patients. Systemic reactions were classified according to WHO guidelines (12). A systemic reaction occurred in 10.9% of patients and the planned maintenance dose was achieved in only 75%, although the cluster schedule had to be interrupted in 44 out of the 48 patients with systemic reactions (12 patients had to discontinue immunotherapy and 32 had to change to conventional buildup). However, in our experience only 6 patients (1.4%) had any systemic reaction, and the cluster schedule could be achieved in all of them. These discrepancies might be explained due to differences in the standardization of extracts in the United Stated and Europe, to the fact that in our schedule the initial dose of therapeutic extract was closer to the final dose, we used a hypoallergenic extract and also, only two doses per visit were administered.

Some risk factors have been reported to be associated to systemic reactions when using cluster schedules (14-17). One of those factors is previously known bronchial asthma. This diagnosis was present in 52.5% of the study population (46.9% of adults and 63.7% of children; p=0.0008). Although the 6 patients in which these systemic adverse reactions occurred had already been diagnosed with asthma, they only represented 2.6% of all the asthmatic patients, their severity was mild and none of them had to have their schedule modified. So, our results back the fact that if bronchial asthma is correctly stabilized and controlled before initiation of subcutaneous treatment (17), cluster SCIT can be safely used.

In spite of the fact that the proportion of children diagnosed with asthma was significantly higher than in adults, there was only one systemic pediatric reaction. Our results confirm the conclusions reported by Schubert et al (18) that observed that the use of a cluster schedule in patients diagnosed with dust mite IgE-mediated bronchial asthma had a safety profile similar to a conventional administration schedule, with an incidence of systemic reactions of 5%. Although in our experience only 1 (0.6%) out of 174 children had a systemic reaction, this may be due to the fact that Acaroid® is an aldehyde-modified extract that reduces allergenicity and hence, improving safety, whereas the therapeutic extract used in the former study was a depot one, what makes us to consider Acaroid® adequate for both adults and children.

Likewise, even though an age below 14 has also been associated to a higher risk of systemic reactions when using cluster immunotherapy, our results let us consider that patients' age did not seem to involve a special risk for systemic reaction associated to the use of Acaroid® with cluster schedule.

A third potential risk factor for systemic reactions is the degree of skin sensitivity previous to the start of treatment with the allergenic extract (15). All our patients had a positive prick test to the allergens included in the assessed therapeutic extract but a later assessment of the skin reactivity of patients that had presented any systemic reaction did not show differences compared to patients without them.

Although being an open retrospective study might have biased the objective assessment of the possible adverse reactions, it has also to be taken in mind that since both the efficacy and safety of this allergenic extract have already been demonstrated in randomized double-blind, placebo controlled trials, the primary goal of this study was to determine the safety and tolerance of this high dosed allergoid within the real routine clinical practice of participating physicians (19, 20). From another standpoint, the involvement of 43 different investigators let us consider the potential heterogeneity of criteria for assessment and also the different profiles of sensitization for different geographic areas.

A prospective 4-year follow-up study on 1738 patients on the safety of conventional immunotherapy (60,785 doses) with biologically standardized allergen extracts from differ-

ent manufacturers (21) reported systemic reactions in 57 (3.3%) patients, with 95 episodes (0.2% of total doses). Taking in mind that our study only assessed the initial cluster phase of immunotherapy, in which the risk for adverse reactions is known to be higher, the results of systemic reactions affecting only 6 patients (1.4%), with 9 episodes (0.3% of total doses), show the adequacy of cluster SCIT with Acaroid®.

In conclusion, the results obtained in this study together with the fact that all patients achieved the desired maintenance dose fulfilling the cluster SCIT, support the use of this accelerated schedule with Acaroid®, in view of its favorable safety and tolerance profile under real use when supervised by an experienced physician for the treatment of house dust mite allergy.

Acknowledgements

We wish to thank all the investigators that have participated in this study: Dra. B. Hinojosa; Dr. González Núñez; Dr. M. Rueda; Dr. A. Roger; Dr. R. Lleonart; Dr. Lain Romero; Dr. Navarro; Dr. S. Nevot; Dr. I. Iglesias; Dr. Alvariño; Dr. A. Mazón; Dr. D. Elquotob; Dr. López Usero; Dr. Domenech; Dr. A. Ferrer; Dr. B. Saenz de San Pedro; Dr. MA Muñoz; Dr. Pérez Padilla; Dr. A. Miranda; Dr. ML. Castellón; Dr. A. Alcaraz; Dr. F. Rodríguez; Dr. Martín Gil-Granados; Dr. Pérdomo Gutierrez; Dr. V. Rodríguez; Dr. Armysen; Dr. C. Vidal; Dr. R. Núñez; Dr. I. Luna; Dr. C. Marcos; Dr. M. Fernández; Dr. E. Pérez; Dr. Martínez Tadeo; Dr. I. Sánchez; Dr. V. Matheu; Dr. J. Iglesias; Dr. L. Almeida; Dr. Castillo; Dr. B. Rodríguez; Dr. T. Garriga and nurses that collaborated with them. We also express our gratitude to Dr. C. García-Rey for his technical assistance. This study was sponsored by Merck, SL

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