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Research Article

Observational Study on The Efficacy and Effects in The Quality of Life of Cluster Immunotherapy Schedule in Patients with Asthma Sensitized to House Dust Mites

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ABSTRACT

Background: The conventional schedule administration of subcutaneous allergen immunotherapy (SCIT) for Acaroid®, requires eight weeks to get the maintenance dose. To reduce the duration of the build-up phase, the cluster schedules have been introduced. The objective was to analyze the one-year efficacy of Acaroid® in a cluster schedule, as well as the effect on the patient's quality of life.

Methods: A real-world observational study was designed, with one-year follow-up. Patients 5-65 years-old with allergic bronchial asthma, sensitized to house dust mites and treated with Acaroid®, in cluster schedule 2/2/2 were included. The main efficacy endpoint was the Asthma Control Test (ACT) score at month 12 compared to baseline. The patient's quality of life was measured with the Asthma Quality of Life Questionnaire (AQLQ) and ESPRINT-15 questionnaire.

Results: A total of 81 patients, 55.6% female, were included with a mean age of 29.7 years old. The ACT score from baseline-12 months significantly improved (p=0.003) 1.4 points (95%CI 0.4-2.4). The proportion of patients with a good asthma control increased significantly from baseline-6-12 months (p<0.05). AQLQ (p=0.014) and ESPRINT-15 quality of life domains significantly improved at 12 months.

Conclusions: The cluster schedule 2/2/2 of SCIT with Acaroid® was effective and allowed shortening the build-up phase to three weeks, instead of the conventional schedule of eight weeks. This resulted in the benefit of the patient in terms of comfort and could reduce the costs related to SCIT administration while maintaining patient efficacy and safety of the conventional schedules.

Keywords

Allergen immunotherapy; cluster schedule; allergy; house dust mite.

Introduction

The Allergen Immunotherapy (AIT) is the only etiological treatment for patients with allergy with demonstrated efficacy and safety in patients with asthma and rhinoconjunctivitis [1-3]. The clinical desensitization to the allergen is reached after the administration of increasing doses of specific allergens extracts to the patients for at least three years, but clinical improvements are usually shown along the first year [4-6]. The AIT can be also administered by sublingual, route, but is the subcutaneous (SCIT) the most frequently used in our setting. SCIT, comprises two phases of administration: the build-up phase, with a slow weekly increase in the doses during eight weeks, and the maintenance phase where monthly and same concentration doses are administered for at least three years. The long-term treatment duration and the multiple periodic visits could lead to problems of compliance and, as result, affect the efficacy of the treatment, so any effort to reduce the number of visits will be on favor of the treatment success.

For the completion of the build-up and maintenance phases with Acaroid®, the product analyzed in this study, two concentration vials are available for the SCIT for patients with House Dust Mites (HDM) allergy. The vial A contains 1,000 Therapeutic Units/ml (TU/ml) and vial B contains 10,000 TU/ml [3]. The conventional schedule recommends four increasing doses weekly with vial A, and four with vial B, to reach the maintenance dose of 0.6 ml of vial B (6000 TU), so a total of eight visits in eight weeks are needed [7]. To reduce the duration of the build-up phase, the cluster schedules for SCIT have been introduced, with the administration of two doses on the same day, at a 30-minute interval, in weekly visits. The cluster schedule recommended by the manufacturer in the Acaroid® Summary of Product Characteristics (SPC) is completed in three visits, so in three weeks the maintenance dose can be reached [7].

If the efficacy and safety of the treatment is equivalent in conventional and cluster scheme, then the cluster schedule should reduce from eight to three the treatment visits and should improve the patient comfort and compliance. Few information about the efficacy of the cluster schedule is available for Acaroid® [7-8]. In this study, the one-year efficacy of the SCIT product Acaroid® is explored using a cluster schedule, in patients with allergic asthma due to HDM in the real world, as well as the effect on the patient's quality of life.

Materials/Methods

A real-world observational study was designed, with one-year follow-up of patients with allergic asthma. The study was approved by the Ethics Committee of the Hospital General Universitario de Castellón (22-October-2020; 5/2020) and it was conducted following national regulations and the Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). The study was completed in four immunotherapy units of Spanish hospitals, from June to October of 2020.

The primary objective was to evaluate the efficacy on asthma control of a cluster schedule of SCIT with Acaroid® in patients sensitized to HDM [7].

The selection criteria were: **1)** Patients between 5 and 65 years old; **2)** Diagnosis of allergic bronchial asthma (GINA)9; **3)** HDM hypersensitivity established by diagnostic skin prick testing or positive allergen-specific IgE; **4)** Patients were excluded if they had any contraindication to SCIT described in the Acaroid® SPC7; **5)** Patients, and their parents or legal representatives in the case of minors, have signed the written informed consent form.

Patients started the subcutaneous immunotherapy with Acaroid® in a cluster schedule 2/2/2 administered at day 1, 8 and 15 (Table 1). Time between doses in the same day must be of 30 minutes. During the build-up phase, the patients started the SCIT with two doses of 0.3 ml of the lower concentration vial (Vial A) containing 300 TU (Therapeutic Units). At day 8, doses of 0.1 and 0.2 ml were administered from the higher concentration vial (Vial B) containing 1000 TU and 2000 TU respectively. At day 15 two doses of 0.3 ml of Vial B were injected with 3000 TU. The maintenance phase dose was the maximum tolerated dose that was monthly administered and used to be 0.6 ml of Vial B (6000 TU).

Table 1: Treatment schedule during the build-up phase of the allergen immunotherapy with Acaroid® in cluster administration.

Strength vial	Administration Day	Dose by ml	Allergen doses in Therapeutic Units (TU)
Vial A 1,000 Therapeutic Units/ml	1	0.3	300
		0.3	300
Vial B 10,000 Therapeutic Units/ml	8	0.1	1000
		0.2	2000
	15	0.3	3000
		0.3	3000

The major allergen content of the high-dose HDM allergoid Dermatophagoides pteronyssinus (DP) is 12 µg/ml Der p1 and 10 µg/ml Der p2, and for the high-dose HDM allergoid Dermatophagoides farinae (DF) is 20 µg/ml Der f1 and 15 µg/ml Der f2.10 The SCIT composition could be DF 100%, DP 100%, or mixed (50% of each allergen). Maintenance and rescue medication was administered following the GINA guidelines [9].

The patient age, gender and history of the allergic disease were recorded. The patients completed three visits: baseline, 6 and 12 months.

The main efficacy endpoint was the Asthma Control Test (ACT) score at month 12 compared to baseline. This validated questionnaire contains five questions referred to the last four weeks. Each question has five levels scoring from 1 to 5 points with a total score from 5 to 25 points. ACT scores of 20 or more means a good asthma control. If the scores are 19-16, asthma was not well controlled, and scores of 15 or less represents a very poorly controlled asthma [11-13]. The minimum clinically significant difference between two ACT evaluations is stablished in 3 points [13].

The number of asthma exacerbations at 6 months before baseline visit and at months 6 and 12 of follow-up were registered in the study. The Forced expiratory volume (FEV1) and the exhaled fraction of nitric oxide (EF_{NO}) were determined at baseline, 6 and 12 months with standardized procedures in all participant centers.

For the evaluation of the quality of life as secondary objective, two questionnaires were applied. The Asthma Quality of Life Questionnaire (AQLQ) comprises 20 questions with five response levels scored from 0 to 4. The questions represent four domains (breathlessness, mood, social limitation and worrying) with a global score, and the results are shown from zero to 10 points where lower scores represents better quality of life. A change in score of 0.5 is the smallest change that can be considered as the minimal important difference (MID) [14-15]. The ESPRINT-15 is a quality-of-life questionnaire specific for patients with allergic symptom with 15 questions scored from zero to six points. The questions are grouped into four domains (symptoms, daily activities, sleep, psychological affectation) where the domain score is the mean score. The scores can vary from zero to six points where lower scores also represents a better quality of life. An additional question about the patient's health is scored in five categories [16].

Statistical methods

The main efficacy variable of the study was the assessment of the difference in the Asthma Control Test (ACT) questionnaire score, from baseline before immunotherapy, and twelve months after SCIT. The null hypothesis of the study is that there is no change in the ACT score from baseline to subsequent visits. With a sample of 80 pairs of measurements, the study has a power greater than 99.9% to detect statistically significant changes for a two-sided paired test. The sample calculation assumes that the significant difference should be greater than 3 points with a standard deviation of 1.5 points, this being the minimum effect that must be detected to consider the effect clinically relevant [13]. The mean difference can be estimated with a precision in the 95% confidence interval of plus/minus 0.31 points (Sample Power-IBM-SPSS).

The statistical analysis was performed using the statistical package SPSS version 27.0. Statistical significance was set at 0.05. A descriptive analysis was performed, based on the frequency distribution of the qualitative variables and calculation of the usual values for the quantitative variables (mean, standard deviation, minimum and maximum, and 95% confidence interval). The comparisons between variables were made using the Fisher test or the Chi2 test when the values are expressed as proportions. For the comparison of independent groups in the case of quantitative variables, the student t-test and ANOVA was used or non-parametric tests when applicable. The primary endpoint analysis was based on all included patients who had received at least one dose of SCIT. The LOCF (Last Observation Carried Forward) rules were applied for the substitution of missing data.

Results

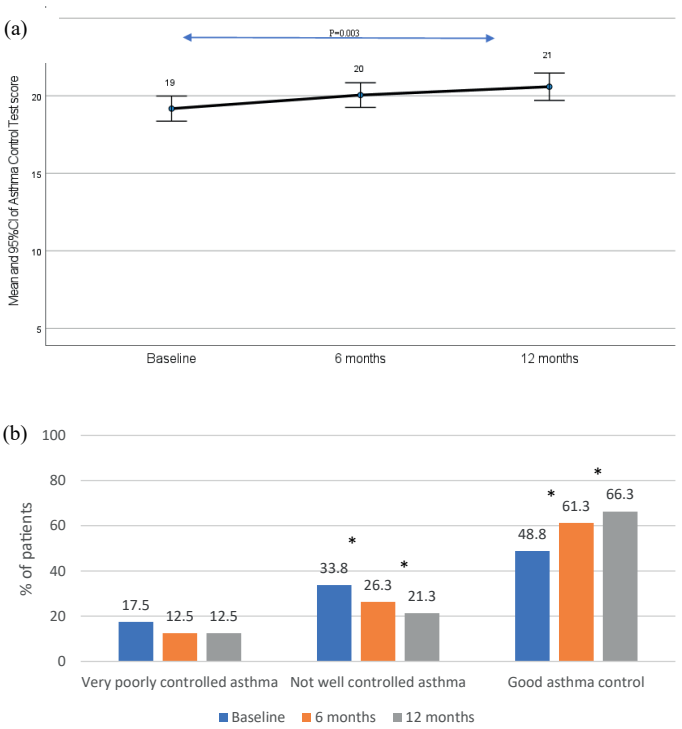
A total of 81 patients were included with a mean age of 29.7 years old (95%CI 26.7-32.7). The demographic and allergic clinical characteristics at baseline are described in table 2.

Table 2: Demographic and allergic symptoms before the subcutaneous allergic immunotherapy of the patients included in the study.

Demographics		**N (%)**
Age group	<12 years	7 (8.6)
	12-17 years	12 (14.8)
	≥ 18 years	62 (76.5)
Gender	Male	36 (44.4)
	Female	45 (55.6)
Allergic symptoms		N (%)
Allergic disease	Asthma only	29 (35.8)
	Rhinitis and asthma	47 (58)
	Conjunctivitis and rhinitis and asthma	5 (6.2)
Asthma classification	Intermittent	27 (33.3)
	Mild persistent	24 (29.6)
	Moderate persistent	30 (37)
Rhinitis classification (n=52)	Intermittent	3 (5.8)
	Persistent	49 (94.2)

The combination of DP 50% and DF 50% was the SCIT composition administered to 61 patients (75.3%), and 20 patients (24.7%) received SCIT with 100% DP.

Figure 1: Asthma Control Test total score and asthma response groups classification from baseline to 12 months of follow-up.



(a) Asthma Control Test (ACT) score at baseline, 6 months and 12 months. (b) Proportion of patients classified by degree of asthma control from Asthma Control Test score: Very poorly controlled asthma refers to ACT scores of 15 or less; Not well controlled asthma refers to ACT scores 16-19; Good asthma control refers to ACT scores of 20 or higher.

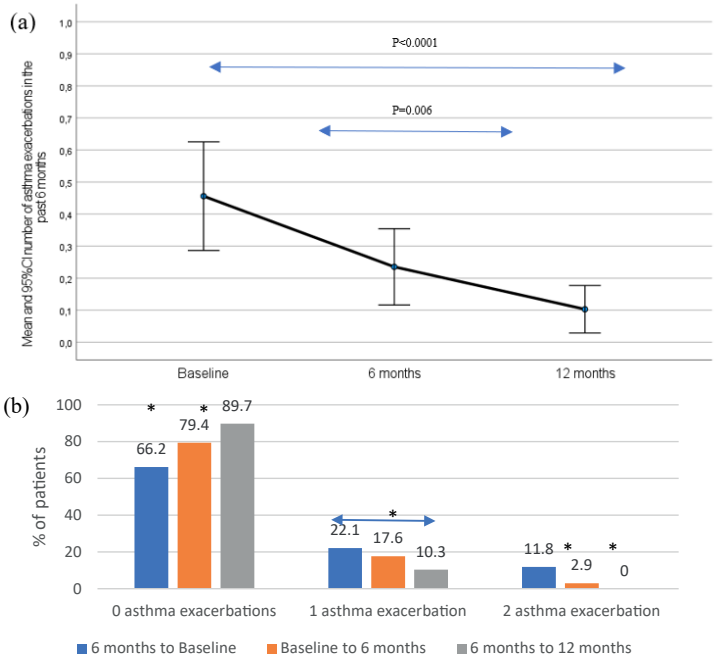
* Statistically significant difference p<0.05.

For the main endpoint of ACT score from baseline to 12 months (Figure 1), a statistically significant improvement was observed (p=0.003) with 1.4 points of ACT score difference (95%CI 0.4-2.4). In the figure 1 is shown that the proportion of patients with a good asthma control increased significantly from baseline to 6 and 12 months (p<0.05), and proportion of patients with a not well controlled asthma was significantly reduced from baseline to 6 and 12 months (p<0.05). The proportion of patients with very poorly controlled asthma decreased but without statistical significance.

FEV1 and EF_{NO} improved in the follow up, but the results were not statistically significant. Baseline FEV1 was 95.2 (SD 1.98) and 99 (SD 1.53) at month 12 (p=0.117). Baseline EFNO was 54 (SD 5.4) and 50.2 (SD 5.9) at 12 months (p=1.00).

The number of asthma exacerbations in the 6 months before baseline period, decreased significantly at 6 months (p=0.006) and at 12-months of follow-up (p<0.0001) as is represented in figure 2. The proportion of patients without asthma exacerbations in the past 6 months increased significantly from baseline to 6- and 12-months periods (p<0.05). The proportion of patients with one asthma exacerbation in the past 6 months, was significantly reduced at 12 months (p<0.05), and the proportion of patients with two asthma exacerbations in the past 6 months decreased significantly at 6- and 12-months periods (p<0.05), as shown in figure 2.

Figure 2: Number of asthma exacerbations and proportion of patients with 0, 1 or 2 asthma exacerbations at each 6 months period.



(a) Number of asthma exacerbations in the past 6 months at baseline, 6 months and 12 months of follow-up.

(b) Classification of the patients by number of asthma exacerbations in the past 6 months.

*Statistically significant p<0.05.

The results of the AQLQ showed the improvements represented in table 3. AQLQ total score significantly improved from baseline to 6 months (p=0.039) and 12 months (p=0.014). Relating the AQLQ domains, only the social limitation score significantly improved at 6 months (p=0.019), and breathless (p=0.048), social limitation (0.005), and worrying (0.018) significantly improved from baseline to 12 months of follow-up. No significant differences were observed in the mood domain from baseline to 6 and 12 months.

The results of the ESPRINT-15 analysis are shown in table 4 and figure 3. The symptoms (p=0.002), daily activities (p=0.012) and sleep (p=0.007) domains significantly improved from baseline to 12 months. Sleep domain also was improved at 6 months (p=0.026). But no significant changes were observed in the psychological affectation domain. A significant increasement of the percentage of patients with excellent-very good and good health status was observed from baseline to 12 months of follow-up (p<0.05), with a decrease of the number of patients with fair or bad health status. No patients with very bad health status were observed (Figure 3).

No systemic adverse reactions were observed. Local reactions were observed but not accounted as were mild and solved in less than 24 hours. A total of 65 patients completed 6 months of follow up (80.3%) with 16 patients lost to follow-up in this period (19.7%), and 60 patients (74.1%) completed 12 months of follow up with five patients lost to follow-up from 6 to 12 months (6.2%). The dropouts were not related to adverse reactions.

Discussion

The objective of this study was to determine if cluster schedule for a specific subcutaneous AIT product (Acaroid®), is effective and improves the patient's quality of life in the real-world clinical practice [7]. The cluster administration shortens the SCIT build-up phase, reaching the optimum maintenance dose in 3 weeks, instead of 8 weeks required with the conventional schedule.

Currently, there are many studies that support the efficacy of allergen-specific immunotherapy for the treatment of IgE-mediated respiratory diseases [1-3]. The efficacy and safety of the SCIT product analyzed in this study, Acaroid® has been demonstrated in several clinical trials [17]. Since the introduction of the cluster administration of allergy vaccines, the results of numerous clinical studies have been published. The conclusion of the studies was that the different schedules used were as efficient and safe as the conventional schedule, without an increase in either the number or the severity of the adverse reactions [8,18-23].

Nevertheless, few studies have analyzed the efficacy of the 2/2/2 cluster schedule of Acaroid®, the cluster regimen recommended in the SPC [8]. In our study, a sample of patients with asthma with a mean age of 29.7 years old, was followed for 12 months, including 23.5% of patients younger than 18 years old. The asthma severity was mild to moderate and persistent in 66.6%, with no patients with severe asthma (Table 1).

Table 3: Asthma Quality of Life Questionnaire (AQLQ): four domains and total score from baseline to 6 and 12 months of follow-up.

AQLQ domain	Baseline Mean (95%CI)	6 months Mean (95%CI)	P (Baseline-6 months)	12 months Mean (95%CI)	P (Baseline- 12 months)
Breathlessness	3.5 (2.7-4.2)	3 (2.2-3.8)	0.103	2.8 (2-3.6)	0.048*
Mood	3.7 (2.9-4.5)	3.1 (2.4-3.8)	0.152	3 (2.2-3.7)	0.074
Social limitation	3.1 (2.1-4)	2.1 (1.5-2.8)	0.019*	1.8 (1.1-2.5)	0.005*
Worrying	2.9 (2.1-3.7)	2.4 (1.8-3)	0.231	2.1 (1.5-2.8)	0.018*
AQLQ total score	3.3 (2.6-4)	2.7 (2.1-3.4)	0.039*	2.5 (1.9-3.2)	0.014*

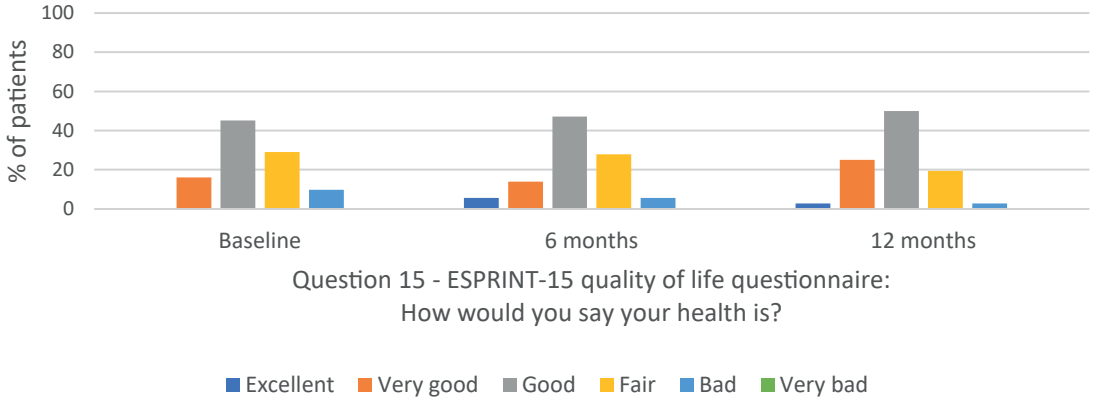
*Statistically significant difference from baseline score.

Table 4: ESPRINT-15 quality of life questionnaire: four domains and total score from baseline to 6 and 12 months of follow-up.

ESPRINT-15 domain	Baseline Mean (95%CI)	6 months Mean (95%CI)	P (Baseline-6 months)	12 months Mean (95%CI)	P (Baseline- 12 months)
Symptoms	3.7 (3.2-4.2)	3.3 (2.8-3.8)	0.212	2.9 (2.3-3.4)	0.002*
Daily activities	2.6 (2.1-3.2)	2.2 (1.7-2.7)	0.275	1.9 (1.4-2.4)	0.012*
Sleep	1.5 (1-2.1)	0.8 (0.5-1.1)	0.026*	0.8 (0.4-1.2)	0.007*
Psychological affectation	1 (0.6-1.5)	0.7 (0.5-1)	0.250	0.8 (0.4-1.3)	0.736

*Statistically significant difference from baseline score.

Figure 3: Health status at baseline, 6 and 12 months as response of the question 15 of the ESPRINT-15 quality of life questionnaire: How would you say your health is?



For the main efficacy end-point ACT significantly improved at 12 months (p=0.003), with 1.4 points of improvement, no reaching the three points of difference for clinical relevance (Figure 1) [13]. Nevertheless, a significative increasement of the percentage of patients with a good asthma control already at 6 months and was even better at 12 months (p<0.05).

The number of asthma exacerbations in the past 6 months was significantly reduced at 6 and 12 months, so, the proportion of patients with two or more asthma exacerbations was reduced by 8.9% at six months and got 0% at month 12. Also, the number of patients with one asthma exacerbation was 11.8% reduced at 12 months (Figure 2).

Although FEV1 and EF_{NO} improved, the results were not significant. This could be due to the ceiling effect in mild to moderate patients. A longer follow-up should be needed to detect improvements in these parameters as shown in previous studies [4].

In this real-world study, we observed significant improvements in health-related quality of life, with a questionnaire specific for patients with asthma, the AQLQ. This improvement resulted already significant at 6 months (p=0.039) and was maintained at 12 months (p=0.014) as represented in table 3. The improvement at 6 months was related to the social limitation domain (p=0.019), and at 12 months all domains, breathlessness, social limitation and worrying, except mood, were significantly improved. Complementary results were obtained with the ESPRINT-15 quality of life questionnaire, where symptoms, daily activities and sleep domains significantly improved at 12 months (Table 4), even sleep was improved at 6 months, but no differences were observed in the psychological affectation domain. The percentage of patients with "Excellent-very good and good health status" significantly improved from baseline to 12 months. The improvement in quality of life of patients with asthma has been reported in published studies completed with the conventional Acaroid® schedule, as soon as after 8 weeks from the start of the SCIT [24,25].

In summary, a significant improvement in the clinical and quality of life efficacy outcomes were seen in the real-world sample of patients included in the analysis, as soon as 6 months after the

initiation of the SCIT with Acaroid® in a cluster schedule and were maintained at 12 months of follow-up.

The study had the limitations of observational studies. The limited sample size and absence of control group did not allow comparative analysis in terms of efficacy and safety.

As conclusion, cluster schedule 2/2/2 of SCIT at high allergen doses of Acaroid® used in usual clinical practice were effective and allowed shortening the build-up phase to three weeks, instead of the conventional schedule of eight weeks. This could result in the benefit of the patient in terms of comfort and treatment compliance and could reduce the costs related to AIT while maintaining patient efficacy and safety as the conventional schedules.

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Competing Interest

Begoña Soler López was contracted by Allergopharma Spain, for the drafting of the publication and management; Nataly Cancelliere was an employee of the study sponsor. The other authors declare no conflict of interest.

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