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Is faster safer? Cluster versus short conventional subcutaneous allergen immunotherapy

Aim: Few studies have compared cluster immunotherapy and conventional administration regimens. The aim of this study was to establish the safety profile of these different regimens in patients with allergic respiratory diseases who received index-of-reactivity (IR)-standardized allergen extracts by the subcutaneous route. **Materials & methods:** The safety of subcutaneous immunotherapy (SCIT), administered by means of a 4-week cluster titration schedule (cluster-SCIT) or by an 8-week short conventional titration schedule (SC-SCIT), both with a target dose of 8 IR, was assessed in a retrospective, observational, multicenter study. **Results:** A total of 658 patients (339 cluster-SCIT and 319 SC-SCIT) were recruited from 92 sites in Spain. Injection site reactions occurred in 25.1 and 27.3% of patients treated with cluster-SCIT and SC-SCIT, respectively. Systemic reactions (European Academy of Allergy and Clinical Immunology criteria) were reported for 0.2% of doses and 1.5% of patients with cluster-SCIT, and 0.7% of doses and 4.4% of patients with SC-SCIT. Most reactions were mild and there were no grade 3 or 4 systemic reactions. No life-threatening systemic reactions, anaphylactic shock, or adverse events leading to therapy discontinuation were reported. **Conclusion:** The safety profile of the cluster regimen supports the use of accelerated SCIT schedules with IR-standardized allergen extracts compared with short conventional schedules, particularly if similar extracts and application methods are used.

KEYWORDS: allergen ■ cluster titration ■ index-of-reactivity-standardized allergen extract ■ short conventional titration ■ subcutaneous immunotherapy

The clinical efficacy of allergen immunotherapy (AIT) is well documented for the treatment of rhinitis [1,2], asthma [3] and Hymenoptera venom anaphylaxis [4]. Therapy usually consists of two phases: an initiation, induction or titration phase in which increasing extract doses are administered at regular intervals until the optimal dose or the maximum tolerated dose is reached; and a maintenance phase in which the highest induction dose is administered periodically for 3–5 years [5].

In real life, during the induction phase, several titration schedules can be used, reaching the maintenance dose in a few hours (ultrarush schedule) or up to several months (conventional schedule).

Conventional schedules are the most widely used regimens and the initial dose is approximately 1000–10,000-fold smaller than the maintenance dose. Although conventional schedules of AIT are considered safe [6,7], their long duration may result in inadequate compliance, or discontinuation of treatment [8–10]. A faster initial dosing regimen may overcome some disadvantages of time-consuming schedules, but the safety profile of these accelerated schedules should at least be similar to that of conventional regimens.

Recent studies with sublingual immunotherapy [11–14] and subcutaneous immunotherapy (SCIT) [15,16] with index-of-reactivity (IR)-standardized extracts have shown that regimens with an accelerated induction or cluster regimen have a good safety profile. Some studies have suggested that cluster immunotherapy may be associated with a similar incidence of adverse reactions as conventional schedules in patients with *Dermatophagoides pteronyssinus*, but direct comparisons in a broad patient population have not been made [17–19]. The aim of this study was to establish the safety of two different regimens of administration (short conventional and cluster) applied to patients with allergic disease who received IR-standardized allergen extracts by the subcutaneous route.

Materials & methods

■ Study population & treatment

In this retrospective, observational, multicenter study, conducted between December 2008 and September 2009, evaluating subcutaneous-specific immunotherapy, 67 investigators were asked to review their medical records and select the first ten consecutive patients of any age with respiratory allergic disease (rhinitis, rhinoconjunctivitis or asthma), with allergic sensitization confirmed by a skin prick test or a specific IgE to any

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aeroallergen (house dust mites, pollen, molds or animal dander), and who had received SCIT with IR-standardized depot extracts adsorbed on aluminum hydroxide (Alustal Rapid®, Stalergenes Ibérica SA, Barcelona, Spain) in the last 3 months. A diagnosis of asthma was based on the criteria of the Global Initiative for Asthma [20]. Data for analysis were extracted from existing patients' files.

Patients were classified into two groups: group 1 patients, who received Alustal Rapid with a 4-week cluster titration schedule (cluster-SCIT); and group 2 patients, who received Alustal Rapid with an 8-week short conventional titration schedule (SC-SCIT). Patients from the cluster-SCIT group received two doses (30 min between doses) each week for 4 weeks, and patients from the SC-SCIT group received one dose each week for 8 weeks, according to the titration schedules in TABLE 1, to a target daily dose of 8 IR (usual maintenance dose) [21]. Patients continued to receive 8 IR every month as the maintenance dose. All patients were treated in the hospital setting; the cluster SCIT schedule was performed under the supervision of the investigator in Hospital Immunotherapy

Units, and the SC-SCIT schedule was administered either in Hospital Immunotherapy Units or in Primary Health Care Centers under medical supervision. AIT administration was carried out according to the European Academy of Allergy and Clinical Immunology (EAACI) recommendations [22], that is, allergen-specific immunotherapy after allergy diagnostic procedures and symptom control with drug therapy followed by patient education and drug therapy adjustment. Based on national and international guidelines, no prophylaxis for adverse events (reactions and side effects) was given to any patient [5,22].

The study was conducted according to the Council for International Organizations of Medical Sciences International Guidelines for Ethical Review of Epidemiological Studies [101]. Confidentiality of patients was strictly maintained. According to local regulations, ethics committee approval was not required for this type of study at the time of data collection.

■ Outcome measures

The primary end point for this study was safety based on adverse events recording. Data

Table 1. Dosing schedules used during the induction phase of subcutaneous immunotherapy.

Day	Vial concentration (IR/ml)	Volume (ml)	Daily dose (IR)	Cumulated dose (IR)
Cluster-SCIT*				
0	1	0.3 + 0.5	0.8	0.8
7	10	0.1 + 0.1	2	2.8
14	10	0.2 + 0.2	4	6.8
21	10	0.4 + 0.4	8	14.8
28	–	–	–	–
35	–	–	–	–
42	–	–	–	–
49	–	–	–	–
SC-SCIT				
0	1	0.1	0.1	0.1
7	1	0.2	0.2	0.3
14	1	0.4	0.4	0.7
21	1	0.8	0.8	1.5
28	10	0.1	1	2.5
35	10	0.2	2	4.5
42	10	0.4	4	8.5
49	10	0.8	8	16.5

*Administered in two injections per day with a 30-min interval between the injections.
 IR: Index-of-reactivity; SC: Short conventional; SCIT: Subcutaneous immunotherapy.

concerning adverse events (local and systemic adverse events) during the titration phase were extracted from existing patients' files and coded according to the most recent EAACI guidelines published in 2006 [22] and the Medical Dictionary for Regulatory Activities [23]. The intensity of adverse events (classified as mild [symptoms that can be easily tolerated, do not interfere with daily activities and are not clinically relevant], moderate [symptoms that cause discomfort but are tolerable, can interfere with daily activities and may be clinically relevant] or severe [symptoms that considerably affect daily activities and are clinically very relevant]), causal relationship to treatment and action taken were also analyzed. The relationship of adverse reactions to patient data (sex, age and allergic disease) and extract composition (pollen, mites, others) were also analyzed.

■ Statistical analysis

In a previous prospective multicenter study conducted in Spain involving 280 patients per group, SCIT administered by a conventional schedule induced systemic adverse reactions in 3.7% of patients. The sample size (280 patients per group) was calculated to ensure an accuracy of 2.0%, assuming that 3.0% would develop an adverse reaction [24].

All variables were analyzed using descriptive statistics, with mean, median, minimum, maximum and standard deviation for quantitative variable; and frequencies and percentages for qualitative variables. The rate of adverse reactions (local and systemic) was expressed as number of reactions per patient and number of reactions per dose. Comparison between groups was performed with Pearson's χ^2 -test. The level of significance used was $\alpha = 0.05$ (two-sided). All data were analyzed using SPSS version 11.0 statistical software.

Results

■ Demographic & anamnesis characteristics

Of the 666 patients included in the study, 658 patients (339 cluster-SCIT and 319 SC-SCIT) had valid data: eight were excluded because, after central review of the data, either they failed to meet the inclusion criteria (i.e., respiratory allergic disease history, sensitization detected by a prick-test or specific IgE, and use of AIT by rapid regimens) or no safety data were available. The age, sex and clinical characteristics of the different groups of patients, according to the build-up

Table 2. Patient demographic and clinical characteristics.

Characteristic	Cluster-SCIT (n = 339)	SC-SCIT (n = 319)
Sex		
Female, n (%)	173 (51.0)	136 (42.6)
Male, n (%)	166 (49.0)	183 (57.4)
Age		
Mean $\pm$ SD (years)	26.2 $\pm$ 13.3	26.7 $\pm$ 13.8
Disease		
Rhinitis, n (%)	156 (46.0)	150 (47.0)
Asthma, n (%)	19 (5.6)	26 (8.1)
Rhinitis plus asthma, n (%)	164 (48.4)	143 (44.9)

SC: Short conventional; SCIT: Subcutaneous immunotherapy; SD: Standard deviation.

schedule used, are summarized in TABLE 2. No significant differences were found between the cluster-SCIT and SC-SCIT populations.

The composition of the allergen extract administered to the different treatment groups is shown in TABLE 3. All patients received a single allergen, except 72 patients (21.2%) in the cluster-SCIT group and 87 patients (27.3%) in the SC-SCIT group (not significant), who received an extract including two or three allergens. *Dermatophagoides* spp. was the most frequent allergen administered in both groups, followed by grass pollen and a mixture of grass and

Table 3. Composition of administered extracts.

Allergen	Cluster-SCIT (n = 339), n (%)	SC-SCIT (n = 319), n (%)
Pollen	148 (43.7)	155 (48.6)
• Grasses	63 (18.6)	49 (15.4)
• Grasses plus olive tree	33 (9.7)	44 (13.8)
• Olive tree	4 (1.2)	6 (1.9)
• Weeds	19 (5.6)	20 (6.3)
• Other trees	5 (1.5)	1 (0.3)
• Others [†]	24 (7.1)	35 (11.0)
Mites	176 (51.9)	146 (45.8)
• <i>Dermatophagoides</i>	163 (48.1)	144 (45.1)
• Others [†]	13 (3.8)	2 (0.6)
Others	11 (3.2)	11 (3.4)
• Molds	8 (2.4)	3 (0.9)
• Animal danders	1 (0.3)	2 (0.6)
• Mixtures [‡]	2 (0.6)	6 (1.9)
Missing	4 (1.2)	7 (2.2)

[†]This category includes mixtures of several pollens (except grass plus olive tree).

[‡]This category includes mixtures of *Dermatophagoides* plus other mites.

[§]This category includes mixtures of mites and/or pollen and/or danders and/or molds.

SC: Short conventional; SCIT: Subcutaneous immunotherapy.

Table 4. Local and systemic reactions per group.

Reactions	Cluster-SCIT* (n = 339)	SC-SCIT* (n = 319)	p-value
Total number of doses	2712	2552	–
Local reactions			
Patients (n)	85	87	ns
Reactions (n)	177	274	–
Patients (%)	25.1	27.3	–
Doses (%)	6.5	10.7	–
Systemic reactions[§]			
Patients (n)	5	14	0.026
Reactions (n)	5	24	–
Patients (%)	1.5	4.4	–
Doses (%)	0.2	0.9	–
Systemic grade 0			
Patients (n)	1	8	–
Reactions (n)	1	13	–
Patients (%)	0.3	2.5	–
Systemic grade 1			
Patients (n)	3	4	–
Reactions (n)	3	8	–
Patients (%)	0.9	1.2	–
Systemic grade 2			
Patients (n)	1 [¶]	2 ^{¶¶}	–
Reactions (n)	1	3	–
Patients (%)	0.3	0.6	–

*A total of 2712 doses were administered.

*A total of 2552 doses were administered.

[§]Grade 0 indicates nonspecific systemic symptoms that cannot be classified as grade 1, 2, 3 or 4; grade 1: mild systemic reactions (localized urticaria, rhinitis or mild asthma; peak flow [PF] <20% decrease from baseline); grade 2: moderate systemic reactions (slow onset >15 min) of generalized urticaria, moderate asthma or both; PF <40% decrease from baseline); grade 3: severe (nonlife-threatening) systemic reactions (rapid onset <15 min) of generalized urticaria, angioedema or severe asthma; PF >40% decrease from baseline); and grade 4: anaphylactic shock (immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor, angioedema, immediate asthma and hypotension, among others).

[¶]Patient identification 207: female 26-years-old with rhinitis. Treatment with Alustal Rapid® three grasses 100%. Late (>30 min after injection) and moderate grade 2 systemic reaction (asthma) at visit two (administration of 2 IR). Relationship: probable. Action taken: not recorded.

^{¶¶}Patient identification 319: male 60-years-old with allergic rhinitis. Treatment with Alustal Rapid five grasses 50% plus four cereals 50%. Late and mild grade 2 systemic reaction (urticaria in thorax and arms) at visit four (administration of 0.8 IR). Relationship: probable. The patient showed the same urticarial reaction, recorded as possible, at visit eight (administration of 8 IR).

^{††}Patient identification 154: female 41-years-old, with allergic rhinitis. Treatment with Alustal Rapid three grasses 50% plus olive 50%. Local and immediate grade 2 systemic reaction after injecting the dose at visit seven (administration of 4 IR). Reaction description, severity and relationship not recorded.

IR: Index-of-reactivity; ns: No statistical significance; SC: Short conventional; SCIT: Subcutaneous immunotherapy.

172 (26.1%) patients (cluster-SCIT, n = 85 vs SC-SCIT, n = 87) experienced 451 local reactions (177 vs 274) and 19 (2.9%) patients (five vs 14) experienced 29 systemic reactions (five vs 24). The incidence of local adverse reactions was similar in both groups (25.1% in the cluster-SCIT group and 27.3% in the SC-SCIT group). The incidence of systemic adverse reactions was lower in the cluster-SCIT group (1.5%; 95% CI: 0.5–2.8) compared with the SC-SCIT group (4.4%; 95% CI: 2.4–6.8; p = 0.026). The systemic reactions were mostly grade 0 (which includes nonspecific reactions according to the EAACI criteria) or grade 1; four (13.8%) were grade 2, and none were grade 3 or 4 (see grade definitions and specific reaction descriptions in TABLE 4). No serious adverse reactions were reported during this study. In both groups, the number of local reactions was similarly distributed across all visits (FIGURE 1). In the cluster-SCIT group, no systemic reactions were reported after injecting the maximal dose (8 IR) on the last visit. In the SC-SCIT group, two systemic reactions were registered after injecting the maximal dose (8 IR) on the last visit (a ‘probably related’ urticarial reaction in a 60-year-old male, and a ‘probably related’ grade 1 rhinitis event not requiring any action). Neither life-threatening systemic reactions nor anaphylactic shock were reported. No adverse events leading to therapy discontinuation were reported.

Local reactions were immediate (within 30 min after administering the injection) in 72.9% of cases in the cluster-SCIT group and in 60.2% of cases in the SC-SCIT group. When analyzing systemic reactions (grouped according to the 2006 EAACI criteria), in the cluster-SCIT group, three of the five reactions were immediate and two appeared after 30 min. In the SC-SCIT group nine were immediate, 11 appeared after 30 min and in four cases the time interval was not registered.

Most of the local reactions were mild, both in the cluster-SCIT group (70%) and in the SC-SCIT group (81.4%), with a very low percentage of severe local reactions in the cluster-SCIT group (1.7%) and none in the SC-SCIT group. There were more systemic reactions in the SC-SCIT group, but there were no severe systemic reactions in either group.

TABLE 5 displays the adverse reactions coded according to the Medical Dictionary for Regulatory Activities. Local injection site reactions were the most frequently reported reactions in both groups (cluster-SCIT, n = 82 [43.2%] vs

olive tree pollen, reflecting seroepidemiology in Spain.

■ Safety evaluation

TABLE 4 summarizes the number and type of reactions reported for the different treatment groups. Based on EAACI criteria, overall,

SC-SCIT, $n = 246$ [85.7%]). In the cluster-SCIT group, seven reactions were systemic (four cases of rhinitis, one of asthma, one of ocular itching and one nonspecific reaction), while in the SC-SCIT group, 25 reactions were systemic, of which rhinitis was the most common (32%), followed by fever (16%) and myalgia (12%). It should be noted that some adverse reactions led to more than one adverse symptom.

Almost all patients in both groups finished the titration schedule as planned (cluster-SCIT 98.2% and SC-SCIT 98.4%). Three patients in the cluster-SCIT group were changed to a conventional titration regimen after suffering from an adverse reaction (one very intense local reaction on three occasions that remained despite a dose decrease, one local reaction on the first day of the cluster regimen for which the patient switched to the conventional regimen, and one very intense local reaction on the first day of dosing that prompted the patient to switch). Dosing was not discontinued and hospitalization was not required in any cases.

In the analysis of the relationship between the incidence of adverse reactions and patient characteristics, in the cluster-SCIT group no statistical differences were found with regard to gender (25.8% for men and 27.2% for women) or presence of asthma (26.8% for asthmatic and 26.9% for nonasthmatic patients). However, patients younger than 18 years of age experienced fewer reactions compared with older patients (19.3 vs 30.5%; $p = 0.03$). In the SC-SCIT group, no significant differences were found with regard to gender (26.2% for men and 31.8% for women), age (34.6% for less than 18 years and 25.8% for older patients), or presence of asthma (29.6% for asthmatic patients and 27.6% for nonasthmatic patients). There were no significant differences between the allergens used for immunotherapy (pollen, mites or other); these showed similar rates of adverse reactions.

Discussion

This retrospective study compared the safety of two different regimens for SCIT administration

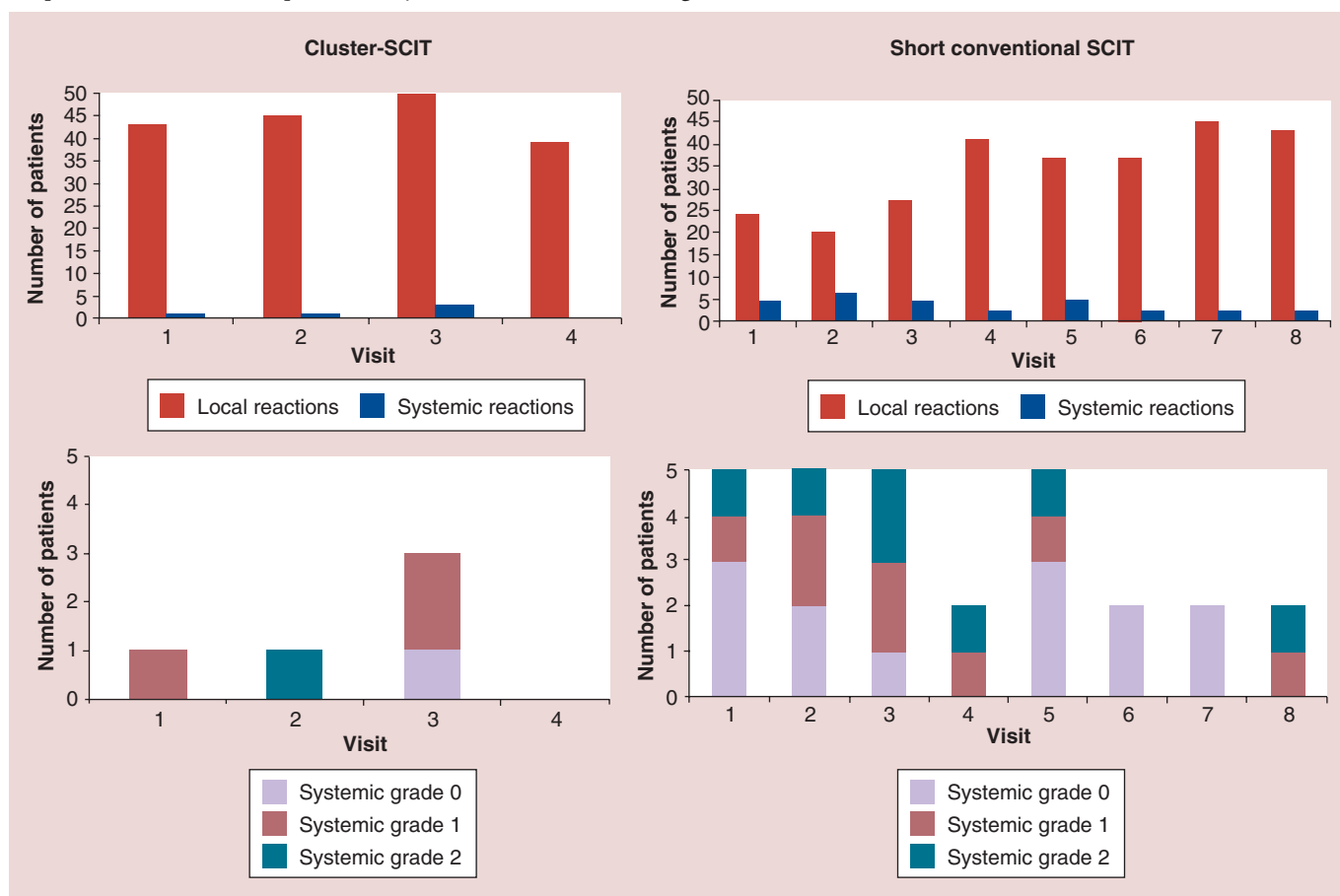


Figure 1. Distribution of local and systemic adverse reactions (grouped according to the 2006 European Academy of Allergy and Clinical Immunology criteria) per group at each visit.

SCIT: Subcutaneous immunotherapy.

Table 5. Description and number of adverse reactions per treatment group, according to the Medical Dictionary for Regulatory Activities classification.

SOC	Cluster-SCIT	SC-SCIT
Local reactions		
Administration site conditions	190 [†]	287 [†]
Systemic reactions		
Respiratory, thoracic and mediastinal disorders	5	9
Ocular disorders	1	1
Skin and subcutaneous tissue disorders	0	2
Nervous system disorders	0	2
Musculoskeletal disorders	0	3
Gastrointestinal disorders	0	2
General disorders	1	6

Total systemic reactions: seven[†] (3.6%); 25[†] (8.0%)
[†]The number of reactions differs from that reported in previous tables because a single drug reaction can cause more than one symptom.
SC: Short conventional; SCIT: Subcutaneous immunotherapy; SOC: System organ class.

in patients with respiratory allergic diseases. In the cluster-SCIT group, systemic reactions were reported for 0.2% of doses and 1.5% of patients. In the SC-SCIT group, systemic reactions were reported for 0.9% of doses and 4.4% of patients. According to a recent Cochrane review based on previous randomized clinical trials, the reported incidence of systemic reactions with conventional SCIT was much higher than in the present study [3]. Reporting of reactions in a clinical trial setting is likely to be considerably higher than in clinical practice. In addition, the clinical trials included in the review generally used aqueous preparations, which are known to have a greater risk of systemic reactions [25]. Our results are in line with the findings of other SCIT observational studies using conventional build-up schedules published within the past 15 years, which reported systemic reactions in 1.1–13.6% of patients [26]. In a multicenter study conducted in 488 patients with rhinitis and/or asthma in 14 allergy departments in Spain, Moreno *et al.* demonstrated that SCIT administered with a conventional schedule induced systemic adverse reactions in 3.7% of patients, similar to our findings [24]. However, two reasons suggest the schedule tested in our study may actually be better. First, in the Moreno study, adverse reactions were monitored during a 2-year period, including build-up and maintenance phases [24], while our study only recorded the reactions during the build-up phase, when there is

a greater risk of systemic reactions [27]. Additionally, the administration schedule used in the aforementioned study (which had 12–14 visits) was longer than the one used in our study (eight visits).

Cluster schedules have been designed to accelerate the build-up phase of immunotherapy, allowing patients to reach the maintenance dose in as little as 4 weeks [28]. The frequency of adverse reactions with cluster schedules also varies between studies, depending on the type of allergen extract, previous knowledge of the optimum dose of allergen, and the time to reach the maintenance dose. With the cluster schedule used in this study, local adverse reactions were present in 25.1% of patients, while systemic reactions were present for 0.2% of doses and 1.5% of patients. Most local reactions (70%) were mild and only three (1.7%) of them were severe. The severity of one systemic reaction was not registered; the three grade 1 systemic reactions were mild and one patient suffered one moderate grade 2 systemic reaction. No drug discontinuation was observed with SCIT. The frequency and severity of systemic reactions were lower compared with those described in most previous studies on cluster schedules [29,30]. This probably occurred because the schedule used in this study (initial dose and time to achieve the maintenance dose) was based on safety data obtained from a previous study that used IR-standardized allergen extracts and showed that the ideal clustered regimen should start at an initial dose no greater than 0.35 IR to minimize the incidence of systemic reactions [15].

An interesting result was the lower incidence of systemic reactions with cluster-SCIT compared with SC-SCIT. Some previous studies comparing conventional schedules with cluster schedules [18,19,31–33] did not show significant differences in the frequency of systemic reactions. Other studies in clinical practice have, however, found higher incidences of systemic reactions with a cluster schedule (10.9% in one retrospective analysis [34] and 10.6% in a prospective Spanish study [35]). In these studies, different extracts and regimens were used. For our study, we hypothesize that the fact that the cluster-SCIT regimen was administered under well-controlled conditions, in hospital settings where allergists carefully evaluated the patients and experienced nurses injected the products, might have contributed to good control and a better safety profile.

One possible limitation of the study is the retrospective design, which could have

increased the variability in data collection. However, we note that all investigators used the same methods to evaluate adverse reactions to treatment, based on the recommendations of EAACI and the Spanish Society of Allergy and Immunology. An additional weakness of the study is the possibility of selection bias owing to the fact that the first ten consecutive patients were included and patients were not randomized to treatment groups. It should also be noted that this was a real life study and the results compare regimens that are already used in Spain (cluster-SCIT and SC-SCIT); a standard conventional regimen is not usual practice in Spain.

For both cluster-SCIT and SC-SCIT groups, the majority of local adverse reactions were immediate whereas a high percentage of systemic late-onset reactions was reported in both groups, which is in line with a previous publication that found that most systemic reactions were late [15]. After investigating possible risk factors predictive of onset of these late reactions during the induction phase of immunotherapy, it was found that aluminum hydroxide, the adjuvant used in depot extracts, was associated with a greater risk of late-onset systemic reactions [15]. Other studies found similar results, indicating that adjuvants used in depot extracts can influence or modulate the adverse effects of immunotherapy [36,37]. Such differences could be due to the physical/chemical features of these molecules affecting the way the allergen is released [36,37]. Therefore, these safety data should not be extrapolated to extracts other than aluminum-precipitated formulations, and only apply to those used in our study.

The frequency and severity of systemic reactions induced by SCIT show a wide variation among different studies, and appear to be dependent on induction regimens, allergens used and certain patient characteristics, such as gender, age or disease [38]. However, in the present study we found no differences between the different allergens used for immunotherapy (pollen, mites or other), and the incidence of adverse reactions was not related to gender, age or disease in any group, except for patients younger than 18 years of age who experienced fewer reactions compared with older patients in the cluster-SCIT group. By contrast, a recently published predictive multivariate model to estimate the individual risk of systemic reactions in patients receiving cluster allergen immunotherapy considered age an

independent risk factor (higher risk in patients over 14 years of age) [35].

In addition to the advantages offered to the patient with rapid schedules of immunotherapy administration (mainly saving time), a previous study comparing both the safety and pharmacoeconomics of conventional and cluster initiation phases of SCIT in 38 allergic patients, found a reduction of costs with the cluster schedule when the cost of the extract, the cost of injections and the time spent were considered [32]. However, the study did not fully account for the specialized and more complex units required for cluster administration, and more complete modeling is needed.

Conclusion

In summary, the safety data obtained from this study suggest that, in spite of a high incidence of mild local reactions, both SC-SCIT and cluster-SCIT regimens have an excellent systemic safety profile, supporting the use of rapid schedules as a good treatment option for patients with allergic respiratory diseases who receive IR-standardized allergen extracts by the subcutaneous route. Use of these administration schedules with other allergen extracts, manufactured and standardized in a different way, would require other studies comparing safety and costs for rapid and conventional regimens.

Financial & competing interests disclosure

This study was supported by Stallergenes Ibérica SA. JL Justicia was an employee of Stallergenes at the time of the study. M García is an employee of Stallergenes Ibérica SA. V Cardona has collaborated as an expert consultant with Stallergenes Ibérica SA. I Dávila has received honoraria from Stallergenes Ibérica as a consultant and speaker. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- This study compared the safety of subcutaneous immunotherapy (SCIT) using index-of-reactivity-standardized allergen extracts administered by means of a 4-week cluster titration schedule (cluster-SCIT) or an 8-week short conventional titration schedule (SC-SCIT), both with a target dose of 8 index-of-reactivity, in patients with allergic respiratory diseases.
- Injection site reactions occurred in 25.1 and 27.3% of patients treated with cluster-SCIT and SC-SCIT, respectively.
- The incidence of systemic reactions was lower with cluster-SCIT than with SC-SCIT (1.5 vs 4.4% of patients).
- Most reactions were mild and there were no grade 3 or 4 systemic reactions or serious adverse reactions.
- The incidence of adverse reactions was not related to gender or the presence of asthma. In the cluster-SCIT group, but not the SC-SCIT group, patients <18-years-old had fewer reactions compared with older patients.
- The safety profile of the cluster-SCIT regimen supports its use as an accelerated SCIT schedule in patients with allergic respiratory diseases.

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▪ of interest

▪▪ of considerable interest

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