

Safety of Two Cluster Schedules for Subcutaneous Immunotherapy in Allergic Rhinitis or Asthma Patients Sensitized to Inhalant Allergens

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Key Words

Asthma · Cluster titration · Rhinitis · Subcutaneous immunotherapy

Abstract

Background: Subcutaneous immunotherapy (SCIT) usually requires a long titration phase, which can be associated with various adverse events (AEs). **Objectives:** It was the aim of this study to determine the safety of 2 cluster regimens for SCIT in patients with allergic rhinitis, with or without mild or moderate allergic asthma, who were sensitized to grass and/or tree pollen, or house dust mites (HDM). **Patients and Methods:** Adult patients were included in a European, open-label, prospective trial. Pollen-allergic patients received grass pollen, grass and olive pollen, or hazel, alder and birch pollen according to a 3-week titration cluster. HDM-allergic patients received HDM extract according to a 2-week titration cluster. The safety of the titration phase was assessed in terms of local and systemic AEs. **Results:** The safety analysis included 157 patients: 110 received pollen and 47 HDM extract. During the cluster titration, 248 AE episodes were reported in the pollen group and 113 in the HDM group; these

were mainly local reactions. Around one third of patients (30.9% pollen and 38.3% HDM) did not experience any AE. In most cases (67.1% of pollen and 71.1% of HDM patients), AEs did not lead to a change in titration schedule. No anaphylactic reaction or other serious life-threatening systemic AEs were reported. Only 2 patients in the HDM group discontinued treatment because of AEs. **Conclusions:** Rapid cluster titration was well tolerated in adults with allergic rhinitis, with or without mild to moderate allergic asthma, due to pollen or HDM. This short-titration, high-dose cluster regime may allow better patient compliance and cost savings.

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Introduction

Specific immunotherapy is traditionally performed by subcutaneous injection of several gradually increasing doses of the sensitizing allergen [1, 2]. The efficacy of subcutaneous immunotherapy (SCIT) has been demonstrated in a number of controlled clinical trials [3–6]. Other studies have investigated short-term hyposensitization schedules designed to reduce the titration phase and in-

crease patient compliance [7–9]. Cluster regimens are an interesting option in this respect as they offer a shorter initial build-up phase with a lower rate of adverse events (AEs). Cluster schedules were first used with *Hymenoptera* venom and were then applied to specific immunotherapy with inhalant allergens [10]. Nevertheless, many different cluster schedules have been published, and the optimal regimen ensuring the shortest ‘time to maintenance dose’ without an unacceptable rate of AEs has not yet been defined. This study was carried out to evaluate the safety of 2 SCIT cluster regimens in patients with allergic rhinitis, with or without mild or moderate allergic asthma, who were sensitized to grass pollen, tree pollen, or house dust mites (HDM).

Patients and Methods

Patients

This multinational, prospective, open-label trial enrolled 157 adult patients (aged 18–55 years) between October 2003 and January 2005 in 8 centers in 5 countries (Germany, Italy, Spain, Portugal, Switzerland). The patients were chosen by the discretion of their allergist according to the following criteria: (1) diagnosed as having IgE-mediated grass pollen, olive and grass, tree pollen or HDM allergic rhinitis with or without bronchial asthma (Global Strategy for Asthma Management and Prevention program I or II criteria); (2) the existence of a positive skin prick test wheal result with a 5-grass pollen extract, *Olea europaea* extract or a 3-tree mixture extract (Stallergènes, Antony, France); (3) the existence of a positive radioallergosorbent test result or of a CAP enzyme allergosorbent test class 2 or greater (≥ 0.7 kU/l).

Exclusion criteria included previous immunotherapy within the past 3 years, other allergies that might interfere with the study treatment, treatment with β -blockers, and patients who were pregnant, planning pregnancy, or lactating.

All patients signed an informed consent form before entry into the trial. The study was approved by the respective ethics committee of each center.

Specific Immunotherapy

Pollen immunotherapy consisted of either a 5-grass mixture (*Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Anthoxanthum odoratum*; 20% each), a combination of olive and grass (50% *O. europaea* and 50% 3-grass mixture: *D. glomerata*, *L. perenne* and *P. pratense* together), or a 3-tree mixture (*Coryllus avellana*, *Alnus glutinosa* and *Betula alba*; 33% each). HDM extracts consisted of *Dermatophagoides pteronyssinus* and *D. farinae* (50% each). All extracts were adsorbed on aluminium hydroxide gel for specific immunotherapy and were supplied by Stallergènes. The allergenic activity of the extracts was evaluated by RAST inhibition [4, 11] in comparison with an in-house reference preparation in *in vitro* and *in vivo* tests and was expressed as an index of reactivity (IR) which was defined as follows: the in-house reference preparation (100 IR) was defined as the concentration eliciting a mean wheal diameter of 7 mm on skin prick tests in 30 allergic patients, determined from a log-log

Table 1. Major allergen content of the allergen extracts used [11]

Allergen	Major allergen	Biological standardization by company	$\mu\text{g/ml}$
5 grasses	Phl p 5	100 IR/ml	7
Birch	Bet v 1	100 IR/ml	50
Mites	Der f 1	100 IR/ml	50
Olive	Ole e 1	100 IR/ml	10

Table 2. Summary of the doses of allergens given and the administration schedules

Cluster	IR/ml	Dose, ml	IR/cluster	IR total
1	0.1	0.1 0.3 0.6	0.1	0.1
2	1.0	0.1 0.3 0.6	1.0	1.1
3	10.0	0.1 0.2	3.0	4.1
4	10.0	0.4 0.8	12.0	16.14
Cluster 1–4 for pollen; cluster 2–4 for mites.				

dose-response curve as a function of allergen concentration. Table 1 summarizes the major allergen content of the allergen extracts used [11].

Study Design

Patients were divided into 2 groups for SCIT: group 1 included all patients ($n = 110$) with allergy to grass pollen, olive and grass pollen, or to hazel, alder and/or birch pollen; group 2 included all patients ($n = 47$) with allergy to HDM.

Three injections were administered on the first injection day (0.01, 0.03 and 0.06 ml) and on the second injection day (0.1, 0.3 and 0.6 ml), with an interval of 60 min between injections and 1 week between injection days. Two injections were administered on the third (1 IR and 2 IR) and fourth (4 IR and 8 IR) injection days. Time intervals were similar to those on the first 2 injection days. Group 1 (pollen group) received a 4-day injection cluster titration, while group 2 (HDM group) received only the last 3 regimens. A summary of the doses of allergens given and the administration schedules is given in table 2.

Monitoring of AEs

Following the recommendations of the European Academy of Allergology and Clinical Immunology [12], all patients were

Table 3. Baseline characteristics of patients given specific immunotherapy for allergic rhinitis or asthma

	Pollen (n = 110)	HDM (n = 47)
<i>Patient demographics</i>		
Age, years		
Mean $\pm$ SD	32 $\pm$ 10	27 $\pm$ 6
Range	18 – 55	18 – 48
Gender		
Male/female	61/49	24/23
Male, %	55.5	51.1
<i>Clinical symptoms</i>		
Rhinitis	110 (100)	47 (100)
Mean years of symptoms	9.3	9.4
Conjunctivitis	109 (99.1)	33 (70.2)
Mean years of symptoms	9.0	8.4
Allergic asthma		
No	34 (30.9)	18 (38.3)
Mild	62 (56.4)	27 (57.4)
Moderate	14 (12.7)	2 (4.3)
Mean years of symptoms	8.2	9.5
PEF, l/min		
Mean $\pm$ SD	491 $\pm$ 114	509 $\pm$ 115
Range	175 – 740	310 – 828

Figures in parentheses are percentages. PEF = Peak expiratory flow.

Table 4. Distribution of the levels of allergen-specific serum IgE antibodies (kU/l)

Pollen class	Hazel, alder, birch	Grass and olive pollen	Grass pollen	<i>D. pteronyssinus</i>	<i>D. farinae</i>
Class 0	2	0	0	0	0
Class 1	2	0	1	0	0
Class 2	16	22	5	5	7
Class 3	42	30	3	13	12
Class 4	34	29	9	15	9
Class 5	9	16	1	6	6
Class 6	3	12	3	8	3

Multiple entries possible according to polysensitization of patients.

monitored by a physician for 30 min after each injection. None of the patients received preventive pharmacological treatment.

The primary objective of this study was to determine the safety of the 2 cluster titration regimens. Before each dose and 30 min after each dose, the patient was asked whether he or she had experienced any AEs, and a physical examination to look for any systemic reactions was carried out. Peak expiratory flow was mea-

sured in asthmatic patients before starting titration and 30 min after each titration step. The last visit was performed almost 2 weeks after the last cluster and at the latest on the day of the first maintenance dose.

Side effects of the cluster therapy have been treated according to the recommendations of the European Academy of Allergology and Clinical Immunology [12]: (1) rhinitis symptoms with antihistamines (peroral, p.o.) and/or topical drugs; (2) mild urticaria with antihistamines (p.o. and parenteral) and/or topical drugs; (3) systemic dermal reactions (urticaria, angioedema) with antihistamine (p.o. or parenteral) or corticosteroids (p.o. or parenteral); (4) mild or moderate bronchial obstruction with β_2 -agonist inhalations and, in severe cases, of bronchial obstruction (forced expiratory volume in 1 s <50% of predicted value) with adrenaline spray (10–20 puffs) or with β_2 -agonists (0.5 mg/ml) subcutaneously or intravenously.

All AEs were classified according to the European Academy of Allergology and Clinical Immunology guidelines [12].

Statistical Analysis

Descriptive data are expressed as frequency and percentages, and mean scores were calculated where appropriate. Nominal data, including dichotomous data, are described by frequency and percentages. Interval data are expressed as the mean, standard deviation and range.

Results

Study Population

One hundred and ten patients with a mean age of 32 $\pm$ 10 years and a slight male predominance (55.5%) were included in the pollen group; 39 patients received tree extracts, 52 received grass and olive extracts, and 19 received grass only extracts. All patients of the pollen group reported allergic rhinitis, and 99.1% additionally suffered from allergic conjunctivitis. Symptoms tended to persist for more than 9 years. Two thirds of patients in this group had suffered mild or moderate asthma for a mean duration of 8.2 years.

Forty-seven patients with a mean age of 27 $\pm$ 6 years were included in the HDM group. All patients of the HDM group suffered from allergic rhinitis, and 70.2% had conjunctivitis, too. The mean persistence of symptoms is 8–9 years. Mild or moderate asthma was present in 61.7% of these patients, for a mean duration of 9.5 years.

All 157 patients were included in the intent-to-treat population used for the safety analysis. The baseline characteristics of these patients are summarized in table 3. In addition, table 4 outlines the levels of allergen-specific serum IgE antibodies in the intent-to-treat population.

Table 5. Number of local and systemic reactions under supervision in the investigators' practices to each allergen in relation to the dose

Dose IR	Pollen				HDM			
	local reaction		systemic reaction		local reaction		systemic reaction	
	none	positive	none	mild	none	positive	none	mild
0.01	108	3	112	0	na	na	na	na
0.03	103	6	109	0	na	na	na	na
0.06	104	5	109	0	na	na	na	na
0.10	109	2	110	0	47	1	48	0
0.30	105	5	110	0	47	2	49	0
0.60	104	10	113	0	46	1	47	0
1.00	103	3	106	0	44	1	45	0
2.00	104	5	108	1	44	1	45	0
4.00	104	0	104	0	46	0	45	1
8.00	103	1	102	0	45	0	45	0

Immediate local and systemic reactions refer to reactions reported while subjects were supervised in the investigators' practices, between injections and up to 30 min after the last injection. Due to altered titration schedules, the numbers of injections per IR dose in some cases exceed the number of patients in the group. na = Not applicable.

Safety of SCIT Cluster Titration Regimes

A total of 361 AEs were reported: 248 in the pollen group, i.e. 101 (40.7%) in the 3-tree extract group, 121 (48.8%) in the grass and olive group and 26 (10.5%) in the grass only group, and 113 in the HDM group. Serious AEs did not occur. Forty-eight of these AEs developed under supervision in the investigators' practices (table 5), and the other AEs developed as late-phase reactions as reported by the patients.

Approximately, one third of patients in each group experienced no AEs (30.9% of patients in group 1 and 38.3% in group 2). The average number of AEs per patient was 3.26 (range 2.76–6.5) in the pollen group and 3.9 (range 1.0–6.4) in the HDM group. No relationship between asthma severity and occurrence of AEs had been detected during cluster titration.

The most common AEs in the pollen group were local injection site reactions (34.9%), followed by allergic rhinitis (11.9%), asthma attacks (6.7%) and headache (6.7%), common cold (5.6%), allergic rhinoconjunctivitis (5.2%), allergic conjunctivitis (2.0%), nausea (2.0%) and dyspnea (1.6%). Other symptoms occurred only in single cases (1–3 events). Only 2 severe reactions were reported; both of these were injection site reactions.

The most common AEs in the HDM group were injection site reactions (44.2%), followed by allergic rhinitis (15.0%), headache (8.0%), rhinoconjunctivitis (6.2%), as-thenia (6.2%) and asthma attacks (4.4%). The rest ranged

between 2.7 and 0.9% (1–3 cases). Only 4 severe reactions (3.5%) were reported; these included 3 cases of injection site reaction (associated with mild asthma attack in 1 patient and urticaria in another) and 1 case of 'tightness of the chest'.

Local reactions were most common after the 0.6 IR dose in the pollen group and the 0.3 IR dose in the HDM group (table 5). There was a tendency for the first injection of the day to induce fewer AEs than subsequent injections and for the last cluster with the highest dose to induce fewer reactions. Systemic reactions within 30 min of injection only occurred in single cases in each group (table 5).

Delayed systemic reactions after 30 min occurred in 8 cases: 1 case of conjunctivitis (mild) and 6 cases of unspecified symptoms (headache 2; cough 1; nasal congestion 1; vasovagal 1; unspecified 1) in the pollen group and 1 case of rhinoconjunctivitis in the HDM group. Asthma attacks were reported 17 times in the pollen group (15 mild and 2 moderate) and 5 times in the HDM group (4 mild and 1 moderate).

In the pollen group, 26.6% of AEs were considered to be definitely related and 4.0% probably related to study treatment. Injection site reactions made up 91% of the definitely related AEs. In the HDM group, 15.9% of AEs were definitely related and 15.9% probably related to study treatment. Injection site reactions made up 100% of the definitely related AEs.

In most cases (67.1% pollen and 71.1% HDM), AEs did not lead to a change in titration schedule. No patient in the pollen group and only 2 patients in the HDM group discontinued the study because of AEs (both asthma attacks).

Concomitant medication was required for 35.1% of AEs in the pollen group and for 31.0% of AEs in the HDM group, but no patient required hospitalization. In the pollen group, systemic H1 was given most frequently (29.4% of all concomitant medication), followed by topical β_2 -agonist (11%), topical corticosteroids (6.4%), topical H1 antihistamines (3.7%) and others. In the HDM group, systemic H1 was given most frequently (30.2% of all concomitant medication), followed by topical corticosteroids (23.3%), topical β_2 -agonists (10.5%), topical H1 antihistamines (2.3%) and others.

No anaphylactic reaction or other serious life-threatening AEs occurred during the study.

Discussion

The regime period of cluster titration is dramatically shortened compared with conventional SCIT. It has been suggested that the risk of local and systemic AEs such as allergic reactions and anaphylaxis may increase when accelerated or rush schedules are used.

The primary objective of this prospective trial on 157 allergic patients was to assess the safety of 2 cluster titration regimens in allergic rhinitis, with or without asthma, with depot allergen extracts. However, we acknowledge that this trial was not a double-blind, placebo-controlled study. Moreover, this open-label design was chosen to reflect the safety of cluster titration in SCIT under 'real-life' conditions in daily routine. The aim of the study was not to evaluate (early) clinical efficacy in comparison with placebo treatment but to proof the tolerability of an accelerated uptitration schedule (cluster therapy) for the initiation period of SCIT with allergen products on the market in a large cohort of 157 allergic patients.

These regimens were well tolerated, with one third (30.9–38.3%) of patients experiencing no AEs and the remaining subjects reporting mainly mild local injection site reactions; only 6 severe AEs, mainly injection site reactions, were reported, representing 0.4% of all injections. Previous studies have described rare cases of life-threatening AEs including anaphylaxis with cluster regimens [13], but these were not observed in the current study.

The frequency of AEs with cluster regimens varies from one study to another, depending mainly on the type of allergenic extract, previous knowledge of the optimum dose of allergen and time to reach the maintenance dose. The results of our study are comparable with other cluster studies with depot allergen vaccines: in a multicenter study of cluster titration with pollen extract, Moreno et al. [14] described delayed systemic reactions after 1.2% of doses in 9.5% of patients, particularly after administration of the high concentration dose, and suggested that further studies are necessary to determine the optimum dosage schedule. On the other hand, Tabar et al. [15] reported excellent tolerability of cluster immunotherapy with a HDM vaccine. Better tolerability has been described with aluminium-adsorbed depot extracts [13], and these were used in the present study.

We observed a similar systemic AE rate to that reported in a previous study on mite allergies which used a longer immunization cluster schedule [16]. In addition, our results are comparable with those observed in a previous study with a HDM vaccine cluster schedule over 3 weeks [17]. Two studies evaluating grass pollen immunotherapy with 4-week cluster regimens have described a higher incidence of systemic events although all were mild and responded to treatment without withdrawal of immunotherapy [14, 18]. In another study, Tabar et al. [19] evaluated HDM cluster immunotherapy in 29 patients and reported only 1 systemic reaction. Only a few studies with a limited number of patients were published on cluster SCIT with chemically modified allergens (allergoids). With these vaccines, it is feasible to shorten the numbers of injections to reach the maintenance dose. In a single-center prospective, open trial study of 64 allergic patients, a good tolerability of cluster SCIT with allergoid extracts could be demonstrated [20]. A recently published study on cluster SCIT with glutaraldehyde-modified extract mixture of grasses on 21 patients revealed a rate of local reactions of 5.1% (of all injections), with no systemic reactions [21].

Taken together, our data confirm the excellent safety profile of these cluster regimens with both native depot allergens and chemically modified extracts.

Our study population included a large proportion of asthmatic patients (66.9%), particularly in the pollen group (69.1%). The safety of rush immunotherapy in a group of 14 asthmatic patients has been reported previously [22], but conclusions are limited by the small number of subjects. One hundred and five asthmatic patients were included in our study, and the incidence of AEs remained low; only 3 patients suffered an asthma attack

that was moderate in severity, and there were no severe attacks. No relationship between the grade of asthma severity and the occurrence of AEs has been revealed during the cluster titration in our study. In a previous multicenter, prospective monitoring study [23], asthma and HDM allergy were found to be associated and HDM-allergic patients experienced more systemic reactions. This was not observed in our study, although we included fewer patients, especially in the HDM group.

The cluster regimens evaluated in the current study included a titration phase, which has been reduced to a maximum of 3 weeks for pollen and 2 weeks for HDM. The standard schedule usually takes between 12 and 16 weeks [1, 2], but many published schedules have ranged from 4 to 8 weeks [13, 14, 16, 18]. This reduction in the build-up phase may improve patient and clinician compliance and may have a significant economic impact, saving both time and number of doses administered. Savings were recently estimated to be EUR 244.95 per patient in

a 3-week cluster [17], whereas our 2-week regimen in a similar population should result in larger savings without compromising safety.

In conclusion, the high-dose and rapidly titrated cluster regimen was well tolerated, even in the asthmatic population, and the AE rate was comparable with that with other regimens with both native and chemically modified vaccines. AEs were usually mild and were those typically associated with SCIT. This cluster regimen may lead to better patient compliance by reducing the treatment initiation phase and should result in considerable cost savings.

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