

Safety aspects of *Cluster* immunotherapy with semi-depot allergen extracts in seasonal allergic rhinoconjunctivitis

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Abstract In addition to allergen avoidance and pharmaceutical medication, specific immunotherapy (SIT) stands for the third most important mainstay offered to allergic patients. SIT has been widely used in pollen-allergic rhinitis, and clinical efficacy has been validated in several controlled clinical trials. Classic SIT protocols begin with an initial dose-increase period (subcutaneous injections of gradually ascending dosages of the allergen extract in weekly intervals) followed by the dose-maintenance period. However, dosage schedules are not commonly standardized yet. *Cluster*-SIT is an accelerated procedure to achieve the maintenance dose after a shorter time interval by the application of 2–3 injections per treatment day. A total of 395 pollen-allergic patients (173 females, 222 males) aging from 18 to 61 years (mean age 32.6 ± 5.9 years) have been investigated using a *Cluster* schedule for Alutard SQ that allows up dosing up to 100,000 SQ-U in six treatment days (within 5 weeks). The schedule was investigated with regard to the side effects during dosage increase. The total number of systemic reactions was $n = 148$ or 2.05% of all injections. Of these, 119 (80%) were classified as immediate reactions, 27 (18%) were late-phase reactions and 2 (2%) were both

immediate- and late-phase reactions. Of all systemic reactions, 124 (84%) were classified as grade 1 reactions, and 24 (16%) as grade 2. No reactions of grades 3 and 4 occurred. Age, gender and the type of the allergen used had no influence on the frequency or severity of local or systemic reactions. The appearance and amount of adverse side effects in *Cluster*-SCIT is comparable to those in conventional schedules. With respect to safety aspects, this accelerated dosage schedule could turn into an interesting alternative for dosage increase during subcutaneous immunotherapy (SCIT).

Keywords Specific immunotherapy (SIT) · Specific subcutaneous immunotherapy (SCIT) · *Cluster* immunotherapy · Allergic rhinoconjunctivitis

Introduction

Besides allergen avoidance, specific immunotherapy (SIT) by subcutaneous injections with increasing doses of the relevant allergen is the only causal treatment for allergic diseases. Particularly in seasonal allergic rhinoconjunctivitis due to pollen, this therapy is a highly effective treatment option [1–3]. Clear evidence has been confirmed for the clinical efficacy (by more than 90 double-blind, placebo-controlled studies published from 1980 to 2008 [1]), the preventive effects on allergic asthma [4] and new sensitizations [5], long-term duration of therapeutic effects [6] and safety of the procedure [7, 8].

Besides the correct indication, however, the efficacy of subcutaneous immunotherapy (SCIT) is also determined by the individual allergic sensitization, the quality and total dose of the administered allergen extracts, and the application schedule [9].

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In classic SCIT-protocols, allergen extracts are injected subcutaneously in repeated, increasing doses and weekly intervals (dose-increase period). Hereafter, the individual maintenance dose is given in monthly intervals. Various treatment schedules are commonly used [3]. In general, a trend toward shortened therapy can be observed with schedules designed to reduce the titration phase and increase patient compliance [10, 11]. In *Cluster*-SCIT, 2–3 injections per day in weekly intervals are administered [12]. In this way, the time of the dosage-increase phase can be reduced to approximately 1/3. However, many different *Cluster*-dosage schedules have been published and the optimal regimen ensuring the shortest ‘time to maintenance dose’ without an unacceptable rate of AEs is still under discussion [10].

This study was aimed to illustrate the frequency of adverse side effects (therapy-related exaggerated local reactions and systemic reactions) of *Cluster*-SCIT with semi-depot allergen extracts in pollen-allergic patients.

Materials and methods

Patients

This study included 395 patients (173 females, 222 males) aging from 18 to 61 years (mean age 32.6 ± 5.9 years). The study was carried out in accordance with the European GCP criteria and the Declaration of Helsinki and after being approved by the regional ethics committee. All patients gave their informed consent prior to their inclusion in the study.

Inclusion criteria were seasonal allergic rhinitis requiring treatment and at least in its third year, a prick test positive for the respective pollen allergen (ALK, Hørsholm, Denmark), positive proof of specific IgE to pollen allergens (Pharmacia CAP $\geq$ class 2 ≥ 0.7 kU/L), age between 18 and 65 years, and informed consent to participation in all examinations involved in the study [1, 13].

Exclusion criteria were a previous desensitization to the relevant pollen allergen within the past 3 years, presence of a perennial allergy, nonallergic inflammatory nasal pathology, chronic sinusitis, pregnancy, bronchial asthma requiring therapy, urgent indication for ACE inhibitors and β -blockers, active tuberculosis, an autoimmune disorder, immunodeficiency disorder or severe rheumatic disease, a malignant tumor, concurrent participation in other clinical trials, and lacking consent [1, 13].

Drop-out criteria were lack of or insufficient compliance, occurrence of severe adverse side effects or the occurrence of an exclusion criterion during course of the study.

Nasal or paranasal sinus disease was ruled out for each patient by means of nasal endoscopy and A-scan ultrasound of the paranasal sinuses. These methods were chosen to get the best possible information about pathologies within the nose and middle-meatus, maxillary and frontal sinus without causing radiation exposure (as in CT-scan).

Course of the study

The patients were treated with specific immunotherapy for pollen allergens according to the therapy schedules shown in Table 1. The preparation Alutard SQ (ALK, Hørsholm, Denmark) was used as therapy extract. Dosage increase was carried out in accordance with the manufacturer’s recommendations in 16 steps of 20–100,000 SQ-U. However, this dosage schedule was modified into a *Cluster* schedule that allows up dosing up to 100,000 SQ-U within 5 weeks as three injections per treatment day once weekly were given (Table 1, [14]).

The patients received either a mixture of tree pollen (Hazel, Alder, Birch each 33.33%; $n = 191$) or a grass pollen mixture with rye (equal parts of *Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Alopecurus pratensis* and *Secale cereale*; $n = 204$).

In the event of adverse reactions, adjustments were made to the dose and the dosage increase corresponding to a previously determined plan adapted from established guidelines [13, 14, 15] (Table 2).

Recording of adverse side effects

Adverse side effects of the treatment were recorded using a modified grade 1–4 classification according to the recommendations of EAACI [13] (Table 3). Local and systemic reactions were categorized according to their chronological appearance in immediate-type reactions (within 30 min after injection) and late-phase reactions (>30 min after injection).

Table 1 Proposed dosage increase in *Cluster* treatment schedule (ALK, Hørsholm, Denmark), [14]

Treatment day	Applied SQ		
1	20	40	80
2	200	400	800
3	2,000	4,000	6,000
4	8,000	10,000	20,000
5	40,000	60,000	80,000
6 (maintenance dosage)	100,000		

Table 2 Further procedure for dosage increase after side effects (according to [13, 14, 15])

Side effect	Further procedure
Local reactions	
Diameter of the swelling	
5–8 cm	Repetition of the last dose
8–12 cm	Dose reduction 1 step in the dosage schedule
12–20 cm	Dose reduction 2 steps in the dosage schedule
>20 cm	Dose reduction 3 steps in the dosage schedule
Systemic reactions	
Stage 0	Dependent upon the local reaction
Stage 1	Dose reduction 2–3 steps in the dosage schedule, slower increase of dose
Stage 2	Dose reduction 3–5 steps in the dosage schedule, slower increase of dose
Stages 3 and 4	General check of suitability of the patient for a specific immunotherapy. If treatment is continued, start again with bottle 1 as a precaution

Table 3 Record of adverse side effects (according to [13])

<i>Local reactions</i>	
Classification according to the diameter of the swelling	
Degree 0:	<5 cm
Degree 1:	5–8 cm
Degree 2:	8–12 cm
Degree 3:	12–20 cm
Degree 4:	>20 cm
<i>Systemic reactions</i>	
Mild general reaction (Stage 1):	
General reddening of the skin, urticaria, pruritus (in particular on the palms and the soles of the feet), reactions of the mucous membranes (e.g., nose, conjunctivitis); general reactions (e.g., restlessness, headache)	
Moderate general reaction (Stage 2):	
Circulatory dysregulation (blood pressure, pulse change); mild dyspnea; sensation of fear	
Severe general reaction (Stage 3):	
Pre-shock symptoms (severe hypotension, pallor); bronchospasm with severe dyspnea; clouding or loss of consciousness, possibly with bowel movement or urination	
Vital organ failure (Stage 4):	
Manifest anaphylactic shock with failure of vital functions (respiratory arrest/circulatory arrest)	

Results

The total number of patients included into the study was $n = 395$. Out of these, 361 reached the recommended maximum dose of 100,000 SQ-U (91%). The total number of injections was 7,213. The percentage of patients

finalizing the dosage-increase phase without changes in the proposed dosage schedule was 76%.

Changes in the dosage-increase phase were caused by local or systemic reactions (79%), intercurrent diseases (17%) or other reasons (4%).

The total number of increased local reactions ($\geq$ grade 1) was 691 (9.6%). Out of these, 552 (79.9%) have been early reactions, 126 (18.2%) late reactions and 13 (1.9%) early as well as late reactions.

Of all increased local reactions, 581 (84.1%) have been grade 1 reactions, 91 (13.2%) have been grade 2 reactions, 16 (2.3%) have been grade 3 reactions, and 3 (0.4%) have been grade 4 reactions.

The total number of systemic reactions was 148 according to 2.05% of all injections. Out of these, 119 (80%) have been early phase reactions, 27 (18%) late-phase reactions and 2 (2%) early as well as late-phase reactions.

Of all systemic reactions, 124 (84%) were classified as grade 1 reactions (see Table 4) and 24 (16%) as grade 2. No reactions of grade 3 and 4 occurred.

Age, gender and the type of the used allergen had no influence on the frequency or severity of local or systemic reactions.

Discussion

The therapeutic efficacy of SIT with subcutaneous injections (SCIT) of native allergen preparations or allergoids has been shown in several clinical trials [1, 2, 15]. The reduction of drug consumption and the increase of performance or the reduction of absence from work makes SCIT a cost-saving treatment from the economical point of view, as well [16, 17].

In 2006, the most recent position paper from the European Academy of Allergy and Clinical Immunology (EAACI) with standards for practical allergen-specific immunotherapy was drafted [15]. It should be noted that all of the schedules mentioned were developed on the basis of empirical experience. To date, it is not known which is the “optimal” dosage schedule for SCIT. Nevertheless, certain concepts have gained wide acceptance on the basis of particularly favorable results in controlled studies and for this reason are currently called “standard schedules.” According to an expert forum of the World Health Organization (WHO), the standard SCIT schedule consists of a dosage-increase phase and a maintenance phase with individually determined maintenance dose [18]. This is in agreement with the current recommendations valid in Europe [15].

In practice, a principal problem of SCIT consists in patient compliance during the time consuming

Table 4 Frequency of local and systemic reactions in the dosage-increase phase of *Cluster*-SCIT (percentage of all injections)

Reactions	All	Grade 1	Grade 2	Grade 3	Grade 4
Local (LR)	691 (9.6%)	581 (84.1% of all LR)	91 (13.2% of all LR)	16 (2.3% of all LR)	3 (0.4% of all LR)
Systemic (SR)	148 (2.05%)	124 (84% of all SR)	24 (16% of all SR)	0	0

dosage-increase phase. Numerous patients cannot or do not want to have such a time consuming treatment performed for occupational and/or personal reasons. For this reason, shortened SCIT schedules have long been sought [10, 15].

Cluster-SCIT is based on a concept by Norman et al. [19] with 2–3 injections per day administered in weekly intervals in the dosage-increase phase of therapy [12]. The aim of this dosage schedule is to achieve the maintenance dose more rapidly than by the conventional ‘one-injection-per-week’ schedule. “*Cluster* immunotherapy saves time with the cost of a slightly increased frequency of side effects” [15]. However, this specific question (safety of *Cluster* schedules in SCIT) is controversial as published data are not consistent [10, 20–25].

Moreno et al. [24] reported in a multicenter study of *Cluster* titration with pollen extract delayed systemic reactions after 1.2% of all doses in 9.5% of patients. Reactions mostly occurred after administration of the high-concentration dose. The authors therefore suggested that further studies are necessary to determine the optimum dosage schedule in *Cluster*-SCIT [24]. On comparing different schedules, native and depot extracts, Møllerup et al. [25] found better tolerability with aluminium-adsorbed depot extracts and these were used in the present study. With systemic adverse events in 2.05% and increased local reactions ($\geq$ grade 1) in 9.6% of all injections, our study on almost 400 allergic patients revealed a good safety profile of *Cluster*-SCIT with semi-depot allergen extracts in pollen-induced allergic patients. This rate was comparable with the numbers of systemic reactions in another *Cluster*-SCIT trial with depot-grass preparations and a slightly modified schedule [26]. In this double-blind, placebo-controlled study on 44 patients systemic (delayed) reactions in the titration phase occurred in 4 cases (1.4% of all injections in the verum-treated group). Enrolling 18 times more patients in the present study our results support the promising findings of Walker et al. [26] on the safety of this accelerated dosage schedule with depot allergens.

In another study of our group with a *Cluster*-titration scheme of pollen depot allergens, a rate of systemic reactions were found in 1.96% of all injections with 82% grade 1 and 18% grade 2 reactions which additionally underlines our current results with the same *Cluster* schedule [14]. In our prospective study on 110 pollen-allergic and 47 house-dust mite-allergic patients, respectively, a 3-week and 2-week *Cluster* protocol with another depot-allergen extract

revealed comparable results [27]. Good safety profile was also confirmed in a recently published prospective *Cluster* study on 79 patients with persistent allergic rhinitis [28]. In this trial, a total of 129 (increased) local reactions ($\geq$ grade 1) or 10.2% of all injections occurred. The total number of systemic reactions was 40 or 3.2% of all injections (with 92% grade 1 and 8% grade 2 reactions).

Moreover, some studies report on *Cluster*-SCIT with chemically-modified allergens (allergoids). With these vaccines it is possible to shorten the numbers of injections needed for the induction phase of SCIT (4–6 injections). In a *Cluster* protocol the maintenance dose therefore can be reached after 1–2 weeks. A recently published study with glutaraldehyde-modified grass extracts showed a rate of (exaggerated) local reactions of 5.1% of all injections with no systemic reactions. However, only 21 allergic patients were randomized to receive *Cluster*-SCIT in this study [20]. In an open trial of our group on 64 allergic patients *Cluster*-SCIT with depot-allergoids extracts showed local reactions ($\geq$ grade 1) in 15.2% and systemic reactions in 4.3% of all injections [29]. Compared to these results the presented *Cluster* protocol with (native, non-modified) depot-allergen extracts indicates an improved safety.

The officially registered (conventional) up dosing protocol in the induction phase of SCIT with Alutard SQ takes 16 injections, respectively, 16 visits. In our study, the titration phase has been reduced to a maximum of six visits. This accelerated procedure did not reveal an increased frequency of therapy-related side effects. The safety of this *Cluster* protocol was investigated in a prospective, controlled, but open-label trial on almost 400 allergic patients. A weakness of this open-label design can be seen in the fact that a direct comparative group (with a conventional up dosing protocol) or a placebo group is lacking. However, our data from a high number of investigated patients confirmed safety results from other *Cluster* trials with a lower number of patients [10].

Moreover, this accelerated protocol may improve both patient and clinician compliance and may significantly save time and costs. In a recently published study on *Cluster*-SCIT savings were calculated to be 244.95 € per patient in a 3-week *Cluster* protocol compared to the conventional therapy [22].

Taken together, in our study on 395 allergic patients the *Cluster*-SCIT with depot allergens was well tolerated with a rate of local (increased) and systemic reactions

comparable to that with other regimens with both native and chemically-modified depot allergens.

Further trials comparing *Cluster*-SCIT with (native) depot-allergen extracts versus depot allergoids as well as different *Cluster* protocols and prospective, direct comparisons to conventional protocols will be performed at our institution.

Conclusions

The present study investigated safety aspects of an accelerated schedule of SCIT in a *Cluster* protocol with native depot-allergen extracts on almost 400 pollen-allergic patients. Herein, the appearance and amount of adverse side effects in *Cluster*-SCIT was comparable to those seen in conventional schedules. However, the question of safety aspects in *Cluster*-SCIT is still controversial as published data are not consistent in the literature.

With respect to safety aspects, the accelerated dosage schedule presented in this trial could become an interesting alternative dosage schedule for induction therapy during SCIT. This therapy may lead to a better patient compliance by reducing the length of the induction phase of SCIT and, furthermore, may result in considerable cost savings.

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