

Cluster protocols in SCIT: enough evidence for practical use?

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Purpose of review

The review provides a comprehensive evaluation of Cluster schedules in subcutaneous-specific immunotherapy (SCIT) in terms of the safety profile and onset of clinical and immunological effects.

Recent findings

Recent major clinical studies could clearly reveal that Cluster schedules with both (semi-)depot-allergen preparations and chemically modified allergen preparations ('allergoids') are well tolerated therapeutic options in SCIT comparable to the safety profile of conventional build-up schedules. Moreover, preliminary data indicate that these accelerated protocols result in a more rapid achievement of clinical and immunological effects.

Summary

Conventional schedules in SCIT have the disadvantage of both a high expenditure of time and the need for a high patient compliance. In accelerated cluster schedules two to three injections are administered sequentially per treatment day (with an interval of 30 min between the injections) in weekly intervals aimed to reach the maintenance dose of SCIT in a short time interval. Recent studies indicate that these accelerated SCIT protocols result in a more rapid achievement of clinical and immunological effects than conventional schedules. Moreover, the safety profile is comparable between conventional and cluster SCIT.

Keywords

allergic rhinoconjunctivitis, cluster immunotherapy, cluster protocols, specific hyposensitization, specific subcutaneous immunotherapy

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Introduction

Apart from allergen avoidance specific immunotherapy (SIT) represents the only immune-modifying and curative (causal) treatment available for patients with allergic rhinoconjunctivitis [1]. Clear evidence has been widely demonstrated for the clinical efficacy, the long-lasting benefit of clinical effects, the (secondary) prevention of bronchial asthma, the reduction of new allergic sensitization and a good safety profile of subcutaneous immunotherapy (SCIT) [2[•],3,4]. The efficacy of this treatment depends on the specific allergen preparation used, the quality and cumulative dose of the allergen extracts administered and, moreover, the dosage schedule.

In conventional SIT, gradually ascending dosages of the allergen extracts are injected subcutaneously in weekly intervals ('up-dose period') until the individual maximum dose is reached ('dose-maintenance period'). Several dosage protocols have been described which last from several weeks to months for the initial, dose-increase period. Despite the clear benefits of SCIT in allergic

rhinoconjunctivitis and (allergic) bronchial asthma only a few allergic patients subscribe to this treatment [5,6]. For work-related or personal reasons a lot of patients are not willing to have this elaborate medical treatment. Inconvenience is likely the most common reason for not beginning or discontinuing the (conventional) form of SCIT [7,8]. Moreover, this treatment is susceptible for interferences: for example in case of a viral or bacterial infectious disease in the initial up-dose period of SCIT the interval between two injections must be extended. According to the registered (conventional) up-dosing protocol the dose then has to be reduced or the therapy must even be restarted again with the lowest dose [2[•],9].

The aim of accelerated schedules in SCIT like cluster protocols therefore is to reach the dose-maintenance period faster than the conventional method. Hence two to three injections are administered per treatment day (with an interval of 30 min between the injections) in weekly intervals. So the individual maximum dose can be reached after 1–4 weeks depending on the depot-allergen preparations or chemically modified allergen

Figure 1 John Freeman (1877–1962) (with kind permission of Dustri-Verlag Dr Karl Feistle, Deisenhofen, Germany)



preparations ('allergoids') used [5,10]. Principles of accelerated schedules in SCIT have been described first by Freeman [11] [(1877–1962) Fig. 1] in the thirties of the nineteenth century as 'intensive desensitization' (in contrast to what he called 'leisurely' conventional therapy). In this article he reported on a female allergic patient 'who was put through a four day rush' course and 'went and rolled in a hayfield without being able to get a sneeze out of it'. Freeman concluded rightly the advantages of accelerate protocols in SCIT as saving of time, convenience and patient compliance.

Taken together, accelerated SCIT schedules offer therapeutic options to reduce time needed for this therapy by decreasing the number of visits during the dose-increase phase. However, these schedules have not been widely used in Europe and in the US, likely to safety concerns [7]. 'Cluster immunotherapy saves time with the cost of a slightly increased frequency of side effects' (EAACI-task force immunotherapy 2006 [12]). However, this question is debatable as recent studies have suggested that cluster-immunotherapy schedules may be associated with a similar safety profile as conventional ('leisurely') schedules.

The safety profile of conventional schedules in subcutaneous specific immunotherapy

To date, local or systemic reactions after SCIT have been frequently classified to the EAACI-grading from Malling

and Weeke [2^{••},13] (Table 1). Recently, a new classification for systemic reactions related to SCIT has been developed by the World Allergy Organisation (WAO) which uses a 5-stage grading system and will allow better comparisons of systemic reactions between different immunotherapy formulations and schedules in the future [14^{••}]. A major analysis of the incidence of adverse events in 912 patients between 1977 and 1987 revealed a frequency of adverse events of 2.2% with 8.67% of these documented as systemic reactions [15]. In a double-blind, placebo-controlled study on 40 grass pollen allergic patients Walker *et al.* [16] found 1.31% local reactions and 0.42% systemic reactions of all injections. Moreover, a higher rate of both local and systemic reactions was found in the up-dose phase (2.5% respectively 1% of all injections). A large review of 38 SCIT studies with conventional build-up schedules revealed a rate of systemic reactions between 0.05 and 3.2% of all injections and between 0.8 and 46.7% of allergic patients (mean 12.92%) [17].

Life-threatening reactions in SCIT are very rare [18]. The German Paul-Erich-Institute (PEI) registered an incidence of 0.002–0.0076% in not modified allergen preparations and of 0.0005–0.01% in modified allergen preparations ('allergoids') between 1991 and 2000 [19]. The incidence in the subsequent PEI report with data between 2001 and 2005 was comparable [20].

Innovations of subcutaneous specific immunotherapy protocols: cluster schedules

The first controlled cluster protocols were described by Norman *et al.* [21] in the 1980s with 11 injections given in 5 treatment days and therapy intervals of 3 weeks in between. However, these protocols resulted in a high number of adverse reactions which limited the wide clinical use of cluster schedules at that time. These preliminary weak results might be explained by the relative extended interval of 3 weeks between 2 treatment days in this protocol: by this a real immunological effect of dose increase might not be facilitated. As a consequence cluster schedules with shorter intervals of treatment have been developed [22–25,26[•],27,28].

Moreover, it was hypothesized that the sequential multiple application of depot-allergen preparations at 1 treatment day induces an accumulation of allergens with

Table 1 Record of systemic adverse side effects

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)	Preshock 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)

Modified according to the position paper of the EAACI [13].

a consecutively boosted disposal. However, this speculation could not be approved in clinical and experimental studies on cluster SCIT [5]. In contrast, a large survey by Møllerup *et al.* [29] with 650 allergic patients demonstrated a significantly reduced rate of adverse events using a cluster schedule with depot-allergens compared to a cluster protocol with native aqueous extracts.

An overview of selected clinical trials on cluster SCIT is given in Table 2 [25,26•,28,30,31,32•,33•,34••,35].

Safety profiles of cluster schedules in subcutaneous specific immunotherapy

In another prospective, 'open label' study of Serrano *et al.* [30], 91 patients with allergic rhinoconjunctivitis and/or allergic asthma were included. Hereof 46 were sensitized to pollen (*Lolium perenne* and/or *Olea europea*), 38 to house dust mites (*Dermatophagoides pteronyssinus*) and 7 to mold allergens (*Alternaria alternata*). Seventy patients reached this maintenance dose after 5 (to 7) weeks of a cluster schedule. Moreover, 89% of all patients could attain the allergic-specific maintenance dose with this schedule. In this study depot-allergen preparations were used and the rate of local and systemic reactions was comparable with conventional schedules again. Interestingly mite-sensitized patients revealed fewest adverse events in the cluster up-titration.

The good safety profile was attested in a controlled, prospective 'open-label' study of our group with 79 adults sensitized to *D. pteronyssinus* [35]. The total number of large local reactions ($\geq$ grade 1) was $n = 129$ (accordingly 10.2% of all injections), whereas systemic reactions were documented after 40 injections (accordingly 3.2% of all injections). However, 37 (92%) of these reactions were grade 1 and three (8%) grade 2 reactions. Both systemic reactions of grade 3 ('preshock') and 4 ('manifest anaphylaxis') were not found.

A recently published study of 395 patients with pollen-induced allergic rhinitis analyzed the safety profile of a 5-week cluster schedule with another depot-allergen preparation [33•]. This schedule aims to reduce the time needed for the dose-induction phase by 66% in comparison to conventional schedules. However, after 148 injections (or 2.05% of all injections) systemic reactions occurred with a majority of grade 1 and grade 2 reactions (84% respectively 16% of all systemic reactions).

Moreover, the good tolerability of cluster schedules in adult patients has been examined in a large retrospective, observational multicenter study of Serrano *et al.* [32•] on 1147 allergic patients who received a total of 6982 doses. Forty-two systemic reactions (0.6% of all injections) were documented in 39 patients (3.4%).

In a recently published trial allergic children sensitized to house dust mites were randomized in two groups: 20 children were treated with a cluster protocol, whereas 10 children were randomized to a 'conventional' protocol to reach to maintenance dose within 13 weeks [26•]. Importantly to emphasize, only children with coexistent allergic asthma were treated in this trial. Again, there was no significant difference in the incidence of adverse events though the time needed for the dose increment in the 'cluster group' was more than half lower than with the registered schedule in the 'conventional group'.

Chemically modified allergen preparations ('allergoids') were also examined in recently published cluster studies. In the study of Subiza *et al.* [28] with a mixed grass mixture modified by glutaraldehyde large local reactions were found after 5.1% of all injections in a cluster schedule, whereas systemic reactions were not observed. In another large 'open-label' study on 1068 adult allergic patients accelerated protocols with depigmented polymerized allergen extracts were examined. Only a very minor rate of systemic adverse events (0.37%) was documented though the maintenance dose was even reached at the first day of therapy ('ultra-rush') [31].

In summary current controlled studies with both adult and pediatric allergic patients reveal a promising safety profile of cluster schedules comparable with the conventional ('leisurely') schedules of dose increase in SCIT.

Onset of clinical and immunological effects of cluster protocols

In addition to the safety issues described above an advantage of accelerated schedules might be due to an earlier approach of SCIT-related clinical and immunological effects. In the current literature three controlled studies have been published focussing these effects 'head-to-head' in comparison to conventional protocols [25,26•,34••]. In the double-blind study of Tabar *et al.* [25] 239 adult allergic patients with allergic rhinitis sensitized to house dust mites (*D. pteronyssinus*) with or without allergic asthma were randomized in two up-dose schedules. One hundred and twenty patients received a 6-week cluster, whereas 119 patients were randomized to a conventional schedule. This trial featured an interesting study design as placebo injections were administered to the 'cluster patients' after attaining the maximal dose in weekly intervals until the patients in the conventional group attained their maximal dose in week 12. Though the total duration of the dose-increase phase was reduced by 46% in the cluster group compared with the conventional therapy, some clinical (asthma and rhinitis scores in patient diaries) and objective parameters (skin-test reactivity, increase in IgG4 levels) were found 6 weeks earlier in the cluster group than in the conventional group.

Table 2 Selection of clinical trials with cluster protocols in SCIT

Author	Year	n	Study design	Allergen	Treatment interval for induction phase (weeks)	Number of injections in induction phase	Systemic adverse events (% of all injections)	Clinical and immunological outcome measures
Serrano <i>et al.</i> [30]	2004	91	Prospective, controlled, open label	46 Pollen 38 House dust mites (HDM) 7 Alternaria	5	14	2.2	–
Tabar <i>et al.</i> [25]	2005	Cluster = 120; conventional = 119	Prospective, randomized, placebo-controlled, double-blind comparative	HDM	6 12	16 13	0.15 (no difference between groups)	Rhinitis and asthma-symptom scores skin-test reactivity, IgG4 and IGE levels
Casanovas <i>et al.</i> [31]	2006	1068	Prospective, controlled, open label	456 HDM, 612 pollen depigmented and polymerized allergen extracts	0 (ultra-rush up-titration)	2	0.37	–
Subiza <i>et al.</i> [28]	2008	Cluster = 22; controls without SIT = 11	Prospective, controlled, randomized open label, comparative	Grass pollen polymerized allergen extracts	1	4	0	Titrated nasal provocation test (after 6.5 injections mean) (cluster-group versus controls)
Serrano <i>et al.</i> [32*]	2009	1147	Retrospective, observational	218 HDM, 231 grasses, 640 grasses and olive, 53 olive, 5 others	2–5	4–10	0.6	–
Schubert <i>et al.</i> [26*]	2009	Cluster = 20; conventional = 10	Prospective, controlled randomized, comparative, open label	HDM, children with allergic asthma 'head-to-head' comparison	5 13	14 14	3.5 4.6	Blocking CD63 expression cysteinyl leukotriene level IgG and IgG4 levels
Pfaar <i>et al.</i> [33*]	2009	395	Prospective, controlled, open label	Pollen	5	16	2.05	–
Zhang <i>et al.</i> [34**]	2009	Cluster = 48; conventional = 48	Prospective, controlled, randomized, comparative open label	HDM 'head-to-head' comparison	6 14	14 (cluster) 15	1.0 0.9	(weekly) rhinitis-symptom scores, Medication scores, Rhinitis Quality of Life (RQLO), Global treatment effectiveness (VAS), Skin-test reactivity, IgE levels
Pfaar <i>et al.</i> [35]	2010	79	Prospective, controlled, open label	HDM	3	12	3.2	–

Another study [34^{••}] with a direct, prospective comparison of conventional and cluster schedules with depot-allergen preparations on 96 allergic patients sensitized to house dust mites was recently published. Cluster SCIT resulted more rapidly in both a decrease of allergic symptoms and a reduced need for concomitant medication than did the conventional schedule though this accelerated schedule reduced the interval for the induction phase by 57%. Similar improvements in Rhinitis-Quality-of-Life (RQLQ) and skin-test reactivity were found.

In the study of Schubert *et al.* [26[•]] with mite-allergic children and coexisting allergic asthma significant immunological effects (increase of mite-specific IgG and IgG4 levels) were already measured in the eighth week after the beginning of the cluster schedule which were demonstrated in the conventional group not earlier than 12 weeks after the beginning of therapy. These data were confirmed by blocking CD63 expression as well as release of cysteinyl leukotrienes after in-vitro basophil stimulation [26[•]].

In another study [28] (early) clinical effects of cluster schedules with chemically modified allergen preparations ('allergoids') were evaluated. In this controlled, randomized, open-label study 22 grass-allergic adults received a cluster immunotherapy. Eleven patients were enrolled as comparators without SCIT. A preseasonal SCIT with 5–7 injections during a mean period of 2.3 months resulted in a significant increase in the threshold dose in the titrated nasal challenge test. These effects suggest an early onset of clinical efficacy of the accelerated cluster schedule, although this trial was not designed to investigate clinical data in the grass season in comparison to a conventional SCIT-schedule ('head-to-head').

Analysis of cost in cluster protocols versus conventional therapy

In the light of pharmacoeconomic aspects accelerated protocols as cluster schedules might become an interesting alternative option to conventional ('leisurely') protocols. A recently published study of Mauro *et al.* [36] compared both safety and reduction of costs of conventional and cluster-up dosing phase of SCIT in 38 allergic patients sensitized to house dust mites. As in other cluster trials the incidence of adverse events was comparable between conventional and accelerated protocols. Moreover, considering the cost of the extract, the cost of injections and the time spent, the cluster regimen resulted in a global spare of 244.95€ per patient in the build-up phase.

Conclusion

In summary an increasing number of clinical studies on cluster SCIT revealed a convincing safety profile of

cluster protocols with both (native) depot allergens and chemically modified allergen preparations ('allergoids'). As an alternative option for the up-dosing phase of SCIT these protocols account for the desire of patients to abbreviate the total length of SCIT without a higher risk of therapy. This issue is of high importance as inconvenience is likely the most common reason for not beginning or discontinuing the conventional (or 'leisurely') form of SCIT. Moreover, preliminary data suggest that the common cost of SIT could also be reduced by these protocols.

In addition first clinical data from phase II and III studies clearly indicate that clinical and immunological effects begin more rapidly in the accelerated cluster schedule. This finding might be due to a higher cumulative amount of allergens in the first weeks of therapy in accelerated schedules compared with conventional up-dosing protocols.

Taken together both risk–benefit balance and accelerated effects of cluster protocols might turn these schedules to become an interesting SCIT option 'ready for the practical use' in the 21st century.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 269).

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