

Comparative Study of Cluster and Conventional Immunotherapy Schedules with *Dermatophagoides pteronyssinus* in the Treatment of Persistent Allergic Rhinitis

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Key Words

Allergic rhinitis • Cluster immunotherapy • Conventional immunotherapy

Abstract

Background and Objectives: Allergy to house dust mite is one of the most common causes of allergic rhinitis (AR) in China. We sought to compare the efficacy and safety of a 6-week cluster schedule of specific immunotherapy with that of a 14-week conventional schedule for the treatment of subjects with persistent AR. **Methods:** The trial was a prospective and randomized study involving 96 patients with persistent AR, aged 14–60 years, who were allergic to *Dermatophagoides pteronyssinus*. While 48 patients were randomly assigned to the cluster schedule reaching the maintenance dose within 6 weeks, the other 48 were randomly assigned to the conventional schedule reaching the maintenance dose within 14 weeks. Eighty-nine patients completed a 1-year treatment course. While kinetic changes in clinical efficacy and adverse reactions were observed during the

treatment, quality of life, cutaneous reactivity and serum-specific immunoglobulin E to *Dermatophagoides pteronyssinus* were measured before and after treatment. **Results:** The cluster schedule reduced the time to reach the maintenance dose by 57% and caused mild systemic adverse reactions after 1.0% of injections (6.7% of patients), with no differences in comparison with the conventional schedule. Cluster specific immunotherapy led to decreases in clinical symptoms and earlier use of medication than did the conventional schedule. Similar improvements in quality of life and reduced cutaneous reactivity without significant changes in specific immunoglobulin E were observed in both groups after 1 year. **Conclusions:** The cluster schedule is a safe alternative to the conventional schedule with the advantage of achieving clinical effectiveness sooner.

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Introduction

It has been accepted that allergic rhinitis (AR) is a global health problem, with increasing prevalence [1–6]. Although there are insufficient epidemiological data for AR in China, some data hint that AR is a heavy burden on Chinese public health [7, 8]. Published data from the International Study of Asthma and Allergies in Childhood Steering Committee [7] have shown that the prevalence of allergic rhinoconjunctivitis symptoms and other allergic symptoms has varied in 6 major cities (Beijing, Chongqing, Guangzhou, Hong Kong, Shanghai and Urumqi) in China, from 5 to 24%.

As in Western countries [9], allergy to the house dust mite (*Dermatophagoides pteronyssinus*) is one of the most common causes of AR in China, being responsible for over 70% of AR cases in northern cities such as Beijing, and even more in southern cities (unpublished data). Allergen-specific immunotherapy (SIT) is an effective treatment for severe AR [1, 10, 11]. The clinical efficacy and safety of SIT with standardized preparations of house dust mite for the treatment of AR has been well documented [12–16]. SIT involves a build-up (up-dosing) phase, followed by a dose-maintenance phase. In a conventional build-up schedule lasting 12–24 weeks, the frequency of injections ranges from 1 to 2 times a week, with a single injection given at each visit. However, this schedule has the disadvantage of the time needed to reach the maintenance dose, with attendant costs in terms of time and resources, which may be more important for a developing country with lower incomes and greater traffic problems. Meanwhile, limiting the indications for SIT has been recommended in developing countries for reasons relating to public health situations and socioeconomics [1].

Accelerated SIT build-up schedules, such as the cluster schedule, offer the advantage of reduced visits to a treatment center, which saves patients time and expense. Most studies of cluster schedules have set out to determine the tolerance and safety of SIT with different allergen extracts [12–18], whereas few studies have compared the efficacy and safety of cluster schedules versus conventional approaches [19]. To our knowledge, no data have been published in English language journals concerning the efficacy and safety of SIT with a standardized allergen in AR patients from Mainland China. In this study, we used a prospective, randomized, open design to compare the effectiveness and safety of a 6-week cluster schedule with that of a 14-week conventional schedule for the treatment of persistent moderate to severe AR in subjects who were allergic to *D. pteronyssinus*.

Methods

This prospective, randomized, open study was approved by the clinical trials committee of the institute.

Patients

The indication for immunotherapy was established on the basis of the guidelines of the European Academy of Allergology and Clinical Immunology (EAACI) [20] and the World Health Organization (WHO) recommendations [1, 10]. Patients were consecutively recruited from the AR clinic of the Beijing Tongren Hospital. Informed consent to participate in the study was obtained from 96 patients (age range 14–60 years, mean 26.4). All underwent a skin prick test (SPT) with histamine (positive control) and standardized extracts (ALK-Abelló, Hørsholm, Denmark) of the following allergens: *D. pteronyssinus*, *D. farinae*, cat and dog dander, mould mix, American cockroach, grass pollen mix, tree pollen mix and weed pollens. The mean of the largest diameter of the wheal and its perpendicular diameter were recorded as the response to the SPT. The skin test index was the ratio between the response to an allergen and the response to histamine. Mite allergy was confirmed by a positive clinical history of allergy to mite, a positive SPT response to *D. pteronyssinus* (wheal diameter ≥ 3 mm and a skin test index ≥ 0.5) and *D. pteronyssinus*-specific immunoglobulin E (IgE) in serum of ≥ 0.7 kU/l (CAP Pharmacia, Uppsala, Sweden). None of the patients had a positive SPT response to other inhalant allergens, except *D. pteronyssinus* and *D. farinae*. Persistent moderate to severe AR was classified according to the WHO AR classification [1]. All asthma patients were classified as having mild asthma based on the guidelines of the Global Initiative for Asthma (<http://www.ginasthma.com/>). The patients who had previously had allergen immunotherapy have been excluded.

Immunotherapy Schedules

Two schedules (cluster and conventional) were used during the initial build-up phase of immunotherapy (table 1). According to the computer-generated random numbers, 96 patients with persistent AR with or without asthma due to mite allergy were randomly allocated to receive either a cluster ($n = 48$) or a conventional ($n = 48$) up-dosing scheme, lasting 6 or 14 weeks, respectively, followed by a dose-maintenance phase. Once the cluster or the conventional method was determined, it was not changed. The SIT was given with a commercial standardized depot preparation of *D. pteronyssinus* extract (Alutard SQ, ALK-Abelló). This depot extract was adsorbed on aluminum hydroxide and was standardized in SQ units. The highest-concentration vial had an allergenic activity of 100,000 SQ/ml and contained 9.8 $\mu\text{g/ml}$ *D. pteronyssinus*. While only 1 injection was given for each visit in the conventional group, 2 injections (3 injections for the first visit) were given for each visit in the cluster group with a half-hour interval. Then the patients were observed for at least 30 min after the last injection of each cluster. In both groups, the maximum dose of 100,000 SQ was administered at the 6th and 14th week, respectively, and the dosing interval was then gradually increased to 6 weeks and maintained until the end of the first year.

All patients came to the AR clinic for treatment throughout the study period and were pretreated with an antihistamine, 10 mg loratadine (Schering-Plough, Kenilworth, N.J., USA), at least

Table 1. Cluster and conventional SIT dosage schedules

Week	Cluster schedule				Conventional schedule			
	injection No.	vial No.	dose SQ units	total dose SQ units	injection No.	vial No.	dose SQ units	total dose SQ units
0	1 (1)	1	10	1,110	1 (1)	1	20	20
	2 (1)		100					
	3 (1)	2	1,000					
1	4 (2)	3	2,000	7,110	2 (2)	1	40	60
	5 (2)		4,000					
2	6 (3)	3	5,000	22,110	3 (3)	1	80	140
	7 (3)		10,000					
3	8 (4)	4	10,000	52,110	4 (4)	2	200	340
	9 (4)		20,000					
4	10 (5)	4	20,000	112,110	5 (5)	2	400	740
	11 (5)		40,000					
5	12 (6)	4	40,000	212,110	6 (6)	2	800	1,540
	13 (6)		60,000					
6	14 (7)	4	100,000	312,110	7 (7)	3	2,000	3,540
7					8 (8)	3	4,000	7,540
8	15 (8)	4	100,000	412,110	9 (9)	3	8,000	15,540
9					10 (10)	4	10,000	25,540
10					11 (11)	4	20,000	45,540
11					12 (12)	4	40,000	85,540
12	16 (9)	4	100,000	512,110	13 (13)	4	60,000	145,540
13					14 (14)	4	80,000	225,540
14					15 (15)	4	100,000	325,540

Figures in parentheses are visit No.

1 h before each visit. Peak expiratory flow rates were recorded before and 1 h after injections for every asthma patient (Chest HI801, Chest, Tokyo, Japan). Patients were excluded from the study if treatment was interrupted for longer than 5 weeks during the initial phase or longer than 16 weeks in the maintenance phase, or if severe adverse systemic reactions occurred.

Evaluation of Clinical Efficacy

Clinical efficacy was evaluated by grading the severity of disease on the basis of diary cards, quality of life (QOL) questionnaire and with a visual analog scale (VAS) for global treatment effectiveness.

Weekly Symptom Score. Symptoms were scored and recorded by patients on a diary card. By using a 4-point scale (0 = none; 1 = slight, the symptom is clearly present but is not troublesome; 2 = moderate, the symptom is present, it is troublesome but not disabling or insufferable; and 3 = severe, the symptom is severe, disabling and/or insufferable) [15], subjects recorded each of any nasal symptoms (nasal blockage, sneezing, itchy nose and rhinorrhea), eye symptoms (itching, redness and swelling) and lung symptoms (breathlessness, wheezing, chest tightness and cough). Nasal, eye or lung symptom score was the mean value of the related symptoms, respectively. The daily symptom score was expressed as the sum of nose, eye and lung scores. The weekly symptom score was the mean value of the daily symptom scores.

Weekly Use of Medication Score. Medication use was scored and recorded daily [19, 21]. A score of 1 point was assigned to 1 tablet of antihistamine. Each puff with a short-acting bronchodilator or a β_2 -agonist through inhalation was scored as 1 point, respectively; each puff with a nasal steroid (Budesonide Nasal Spray, Astra Zeneca AB, Sodertalje, Sweden) was scored as 0.75 points, and 0.25 points scored for each puff with nasal antihistamine (Azelastine Nasal Spray, Viatrix, Hamburg, Germany). Oral steroid (prednisolone) was contemplated only for severe exacerbations and ascribed a value of 1 point/mg. The weekly use of medication score was the mean value of the daily use of medication scores.

Quality of Life. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) developed by Juniper et al. [22] was used before (baseline) and after 1 year of treatment. The RQLQ was divided into 7 domains: sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, activities and emotions. Each domain was scored between 0 (no impairment of QOL) and 6 (severe impairment). The mean score of all 7 domains gave an overall QOL score.

Global Treatment Effectiveness. The VAS for the objective global effectiveness of the immunotherapy consisted of a 100-mm horizontal line without intermediate marks or signs. The left end was labeled 'very good' and the right end 'very poor'. The patients marked the scale with a cross to evaluate the global efficacy of their treatment since the most recent visit to the treatment center.

Table 2. Demographics and symptom duration for the 2 treatment groups

Treatment group	Cluster group (n = 45)	Conventional group (n = 44)	p value
Age, years	25 (15–36) ^a	25 (12–34) ^a	0.438 ^c
Sex, male/female	22/23	20/24	0.746 ^b
Disease duration, years	5 (3–10) ^a	4 (3–9) ^a	0.535 ^c
Residency, local/non-local	32/13	37/7	0.225 ^b
Asthma, yes/no	7/38	8/36	0.741 ^b
FEV ₁ , % predicted	95 (93–100) ^a	95 (91–100) ^a	0.438 ^c
Symptom score	3.0 (2.5–3.7) ^a	3.6 (2.7–4.2) ^a	0.359 ^c
Medication score	0.54 (0.36–0.7) ^a	0.6 (0.5–0.8) ^a	0.102 ^c
SPT wheal size to <i>D. pteronyssinus</i> , mm	8 (6–9) ^a	8 (6–9.5) ^a	0.639 ^c
Skin test index to <i>D. pteronyssinus</i>	2.0 (1.0–2.1) ^a	2.0 (1.0–2.1) ^a	0.345 ^c
<i>D. pteronyssinus</i> -specific IgE, kU/l	11.0 (3.9–36.5) ^a	16.2 (4.6–33.7) ^a	0.809 ^c

FEV₁ = Forced expiratory volume in 1 s.

^a Median, with interquartile range in parenthesis. ^b χ^2 test. ^c Mann-Whitney U test.

Safety Evaluation

The patients were instructed to immediately report any symptom appearing during the observation period and to contact the physician if adverse reactions occurred. Recording of adverse reactions included time of onset and resolution, previous doses of study medication, severity, treatment undertaken, estimation of a possible relationship to allergen injection, and outcome. Side reactions were classified according the localization (local or systemic) and the time of appearance (immediate or delayed). Local reactions were expressed as the length of the wheal diameter. The immediate reactions with a diameter of <5 cm and the delayed reactions with a diameter of <10 cm were considered clinically irrelevant, because a reduction in dose is not recommended [21]. Systemic adverse reactions were classified in accordance with the standards of the EAACI [20].

Time Course of the Study

Apart from the RQLQ, the parameters of clinical efficacy including weekly symptom score, weekly use of medication score and global treatment effectiveness were evaluated at week 0 (W0, the initiation of immunotherapy), W6 (when the maintenance dose was reached with the cluster schedule), W14 (when the maintenance dose was reached with the conventional schedule) and W52 (after 1 year of treatment), respectively. The RQLQ, specific IgE and skin reactivity to *D. pteronyssinus* were evaluated before (W0) and 1 year after the start of immunotherapy (W52).

Statistical Analysis

Statistical analysis was carried out using SigmaStat for Windows version 2.0. A Kruskal-Wallis one-way analysis of variance on ranks or the Mann-Whitney rank sum test was used to analyze intra-group or between-group differences, respectively, and multiple comparisons versus the control group (Dunn's method) was used to analyze intra-group differences. A χ^2 test was used to determine differences in the rate of adverse reactions. The difference was considered significant at values of $p < 0.05$.

Results

Patients

Of the 96 patients, 89 completed the 1-year treatment study (45 patients in the cluster group and 44 patients in the conventional group). Seven patients (3 in the cluster group and 4 in the conventional group) did not complete the initial phase and were excluded from subsequent analysis. Six patients dropped out because of problems traveling to the immunotherapy unit for scheduled treatment. One patient was withdrawn because she became pregnant. During the maintenance phase, no patient was lost to the study before the end of the first year. The 2 groups were well balanced for demographics, sensitivity to *D. pteronyssinus*, symptom duration and severity, medication scores and forced expiratory volume in 1 s (table 2).

Clinical Efficacy

Generally, weekly symptom scores and use of medication scores in both the cluster group and the conventional group decreased continuously during the 1-year (52-week) treatment (fig. 1, 2).

Weekly Symptom Score. At W6, while the symptoms significantly decreased in the cluster group compared with W0 ($p < 0.05$), no significant decrease was seen in the conventional group. There was a greater reduction in the cluster group (16 vs. 2%, $p < 0.01$). At W14, the symptoms in both groups decreased significantly compared with W0 ($p < 0.05$, respectively). Again, the reduction was greater in the cluster group (30 vs. 20%, $p < 0.01$). From

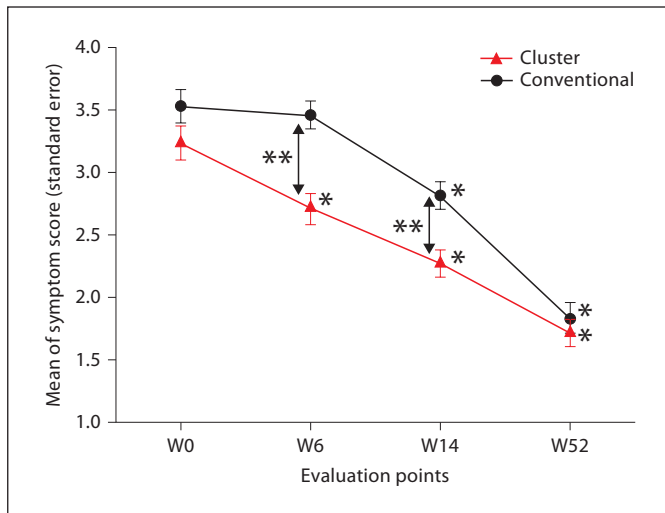


Fig. 1. Weekly symptom score from W0 to W52 in the cluster and conventional treatment groups. * $p < 0.05$, difference from W0 (Dunn's method); ** $p < 0.01$, difference between the 2 groups (Mann-Whitney rank sum test).

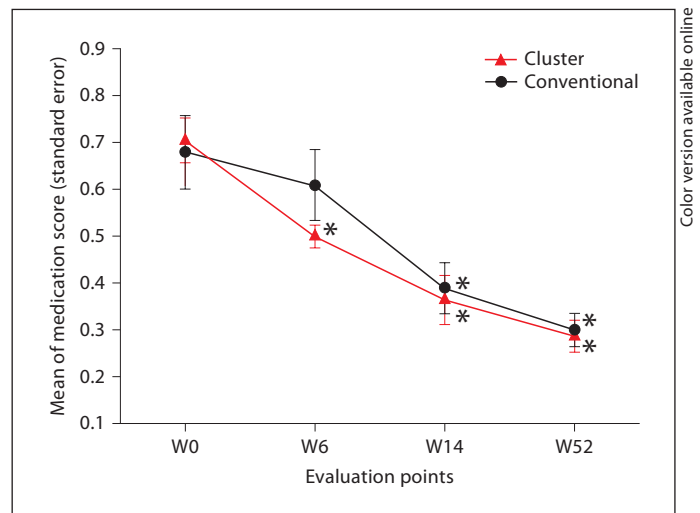


Fig. 2. Weekly medication score from W0 to W52 in the cluster and conventional treatment groups. * $p < 0.05$, difference from W0 (Dunn's method).

W14 to W52, further reduction was greater with the conventional therapy, such that the improvement in symptoms at the end of the observation (W52) was similar in both groups (47 vs. 48%, $p > 0.05$) (fig. 1).

Use of Medication Score. The reduction in medication use was similar for both the cluster and conventional groups at W6 (29 vs. 10%), W14 (48 vs. 43%) and W52 (59 vs. 56%), respectively ($p > 0.05$). At W6, while the use of medication significantly decreased in the cluster group compared with W0 ($p < 0.05$), no significant decrease was seen in the conventional group. At W14, the medication scores in both groups decreased significantly compared with W0 ($p < 0.05$). From W14 to W52, both the cluster group and the conventional group showed a significant reduction in the medication score compared with W0 ($p < 0.05$, respectively).

Quality of Life. The results of the QOL questionnaire are shown in table 3. There were no significant differences between the 2 groups before and after the study (W0 vs. W52). One year on from the beginning of the study, both groups obtained satisfactory improvements compared with the baseline in overall QOL and all other domains, except for non-hay fever symptoms in the conventional group ($p > 0.05$).

Visual Analogue Scale. Generally, VAS scores in both the cluster group and the conventional group decreased continuously during the 1-year treatment course (fig. 3). At W6, VAS significantly decreased in the cluster group

compared with W0 ($p < 0.05$), and no significant reduction was seen in the conventional group (20 vs. 2%, $p < 0.01$). The difference between groups had disappeared at W14 (38 vs. 33%), with obvious reductions in VAS scores in both the conventional group and the cluster group, compared with W0 ($p < 0.05$, respectively). From W14 to W52, both the cluster group and the conventional group had a significant reduction in VAS score, compared with W0 ($p < 0.05$, respectively), and the reductions in the cluster and conventional groups were similar (50 vs. 49%, $p > 0.05$) (fig. 3).

SPT and IgE. At W52, both the cluster and conventional groups showed a significant reduction in skin test index ($p < 0.01$, respectively) and there was no significant difference between the groups (fig. 4). Meanwhile, the specific IgE level did not change significantly in either the cluster group or the conventional group, compared with that of W0, and there was no significant difference between the groups (fig. 5).

Adverse Reactions

All local reactions were immediate and clinically irrelevant (diameter < 5 cm). During the incremental-dose phase, there were 11 local reactions triggered by 1.7% of all injections in 6 patients (13.3% of all patients) in the cluster group and 9 local reactions triggered by 1.4% of all injections in 5 patients (11.4% of all patients) in the conventional group. During the maintenance

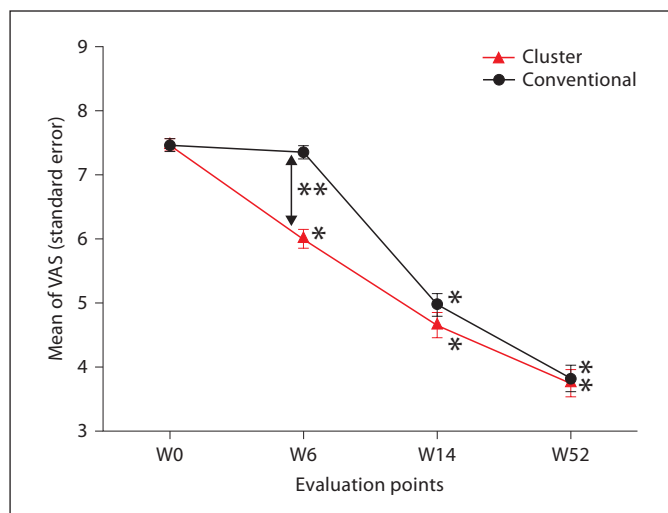


Fig. 3. VAS from W0 to W52 in the cluster and conventional treatment groups. * $p < 0.05$, difference from W0 (Dunn's method); ** $p < 0.01$, difference between the 2 groups (Mann-Whitney rank sum test).

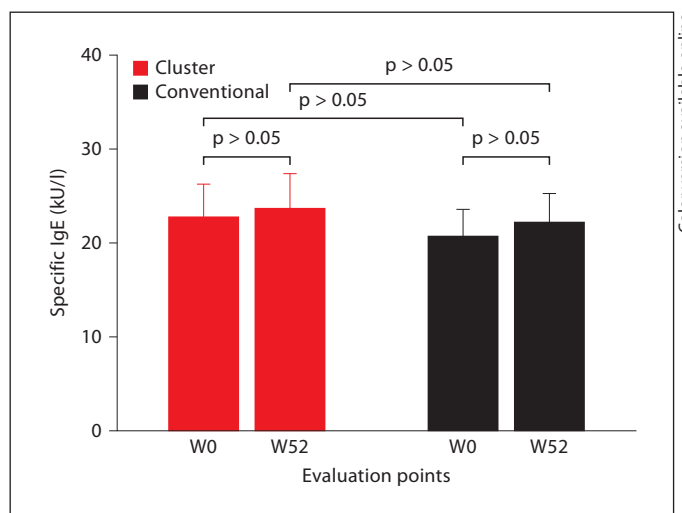


Fig. 5. Specific IgE levels in the cluster and conventional groups at W0 and W52.

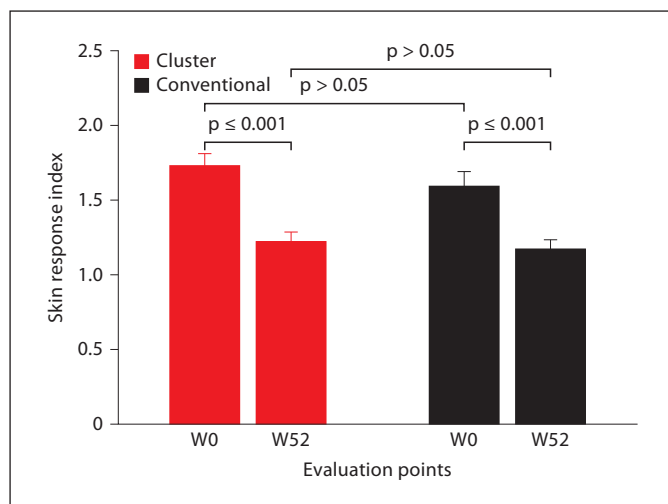


Fig. 4. Skin response index in the cluster and conventional groups at W0 and W52.

phase, there were 7 local reactions in 4 patients in the cluster group and 5 in 4 patients in the conventional group. There were no differences between groups in frequency of local reaction ($p > 0.05$), either during the incremental-dose phase or during the maintenance phase (table 4).

In total, there were 11 systemic reactions triggered by 0.85% of the allergen injections in 6 patients (6.7% of all

patients) during the incremental-dose phase. While 3 systemic reactions graded 1 and 2 reactions graded 2 were observed in the cluster group, 4 reactions graded 1 and 2 reactions graded 2 were observed in the conventional group (table 4). There was no difference between the 2 schedules in frequency or type of systemic reaction ($p > 0.05$). There were 9 systemic reactions triggered by 1.3% of the allergen injections in 5 patients (5.6% of all patients) during the maintenance phase. While 4 systemic reactions graded 1 and 2 reactions graded 2 were observed in the cluster group, 3 reactions graded 1 and 1 reaction graded 2 were observed in the conventional group. Again, no difference between the 2 schedules in frequency or type of systemic reaction was found ($p > 0.05$) (table 4). No grade 3 or 4 reactions occurred during the 1-year course of immunotherapy. All systemic reactions occurred within 20 min of the injection and were successfully treated.

Discussion

The effectiveness of immunotherapy for both seasonal AR [16] and allergic asthma [23] has been well documented. In spite of the clear beneficial effects of immunotherapy in AR, only a few AR patients subscribe to this treatment. This is mainly due to the inconvenience, one of the most frequent reasons for discontinuing treatment or re-

Table 3. Descriptive statistics of the RQLQ, intra-group comparative statistics

QOL	W0	W52	p value ¹
Activities			
Cluster	3.8 (3.5–4.2)	2.5 (1.4–2.9)	0.001
Conventional	3.6 (3.0–4.3)	2.2 (1.4–2.6)	0.001
Sleep			
Cluster	2.4 (2.0–3.5)	1.1 (1.0–1.5)	0.001
Conventional	2.4 (2.0–3.0)	1.4 (1.0–2.0)	0.001
Non-hay fever symptoms			
Cluster	1.9 (1.5–2.7)	1.6 (1.4–2.0)	0.010
Conventional	1.9 (1.5–2.1)	1.7 (1.4–2.0)	0.080
Practical problems			
Cluster	3.5 (3.0–4.0)	2.2 (1.3–2.3)	0.001
Conventional	3.7 (3.2–4.2)	2.1 (1.3–2.4)	0.001
Nasal symptoms			
Cluster	3.7 (3.3–3.9)	2.7 (1.0–2.9)	0.001
Conventional	3.6 (3.1–3.8)	2.6 (2.0–3.0)	0.001
Eye symptoms			
Cluster	1.9 (1.6–2.4)	1.4 (1.0–2.0)	0.003
Conventional	2.1 (1.6–2.5)	1.6 (1.4–1.8)	0.002
Emotions			
Cluster	2.0 (1.8–2.3)	1.2 (1.0–1.5)	0.001
Conventional	1.9 (1.5–2.1)	1.0 (0.7–1.3)	0.001
Overall QOL			
Cluster	3.0 (2.7–3.0)	2.0 (1.5–2.0)	0.001
Conventional	3.0 (2.0–3.0)	1.0 (1.0–2.0)	0.001

Data are medians with interquartile ranges in parentheses.

¹ Wilcoxon test.

fusing it altogether [24]. Six of the 7 patients who withdrew from the study during the treatment complained about the unacceptable traveling time. Most of the local patients involved in the study were located within 50 km of the medical facility and they usually took 1–3 h to reach the treatment center. Patients from the neighboring provinces, located 50–400 km from the medical facility, took from 3 to more than 8 h to travel to the treatment center. While little can be done to alter either the recommended waiting period of 20–30 min in the medical facility after the injections or the request that SIT must be administered in a medical facility, reduced frequency of visiting has the potential to increase patient compliance with SIT. This has more importance in developing countries where inconvenience is primarily due to the time spent in travel.

We used a cluster immunotherapy build-up schedule, entailing administration of 2 injections sequentially for 1 single visit except for the first visit (3 injections), with the

Table 4. Adverse reactions in the cluster and conventional groups

	Cluster group (n = 45)	Conventional group (n = 44)
Incremental-dose phase		
Injections	632	667
Patients with local reactions	6 (13.3)	5 (11.4)
Injections with local reactions	11 (1.7)	9 (1.4)
Patients with systemic reactions	3 (6.7)	3 (6.8)
Injections with systemic reactions	5 (1.0)	6 (0.9)
Grade 1	3	4
Grade 2	2	2
Maintenance phase		
Injections	403	312
Patients with local reactions	4 (8.9)	4 (9.1)
Injections with local reactions	7 (1.7)	5 (1.6)
Patients with systemic reactions	3 (6.7)	2 (4.6)
Injections with systemic reactions	6 (1.5)	4 (1.3)
Grade 1	4	3
Grade 2	2	1

Figures in parentheses are percentages.

maintenance dose being achieved within 6 weeks (7 visits; table 1). Compared with the up-dosing phase of the conventional schedule, which was 14 weeks (15 visits) into the study and entailed administering 1 injection at each visit, the up-dosing phase of the cluster schedule was 57% shorter. Meanwhile, the visit number of the cluster group was 53% less. Although there was no difference statistically, the cluster group had more patients from the neighboring provinces (29 vs. 16%), which hints at better compliance of these patients. The convenience of fewer trips to the medical center might be one of the explanations for that.

For evaluation of the effectiveness of the immunotherapy, the optimal parameters indicating efficacy are reduction in symptoms and/or drug intake [11]. The parameters used in this study were a severity of disease score, diary cards, a VAS and impairment of QOL. After 6 weeks of treatment, while the symptom scores for AR and the use of medication were significantly reduced in the cluster immunotherapy group, the reductions in both symptom scores and use of medication in the conventional immunotherapy group were not significant. This was consistent with the patients' global evaluations of the 2 schedules, respectively (fig. 3). Diary cards and use of medication scores used in a previous comparative study had shown a similar result in that global rhinitis symp-

toms and medication use scores decreased by 43% in the cluster group but showed no decrease in the conventional group during the first 6 weeks of treatment [19]. The absence of efficacy of the conventional immunotherapy might be due to the low dose used for immunotherapy at that point during the treatment schedule (cumulative dose, 312,110 vs. 3,540 SQ units, i.e. about one eighty-eighth the dose given to patients in the cluster group). The efficacy of conventional immunotherapy was not indicated by the significantly reduced scores for both symptoms and the use of medication, until the maintenance dose was achieved after 14 weeks. In patients treated using the cluster schedule, the decrease in AR symptoms at W14 was greater than for the conventional group (fig. 1), although no difference in the use of medication was found (fig. 2). Meanwhile, the patients' global evaluations of the 2 types of immunotherapy were similar (fig. 3). After 1 year of treatment, effects of both schedules on AR symptoms and use of medication were the same. This was consistent with the patients' global evaluations of the treatments using VAS.

On the basis of Mallings' arbitrary grading system to evaluate the general efficacy of immunotherapy [11], there was no efficacy in either the cluster or the conventional schedules at W6 in reducing AR symptoms or medication use, or improved global efficacy of the immunotherapy as evaluated by VAS, since the scores improved by less than 30%. At W14, the effectiveness of both schedules in reducing medication use or improving VAS was low or moderate, although there was still no effectiveness in reducing AR symptoms in either schedule. However, the reductions in all the parameters were less than 60%, which indicated a moderate efficacy of treatment in both of the groups at the end of 52 weeks. This finding is consistent with the results of an earlier comparative study involving both AR and asthma patients [19].

The greatest problem encountered in trying to reduce the frequency of visits for treatment to shorten the up-dosing phase is the potential for saving time at the cost of a slightly increased frequency of side effects [25]. Historically, a wide range of systemic reactions after inhalant allergen injections has been reported in the literature. These range from <1% in patients receiving a conventional schedule, to 27–100% in patients receiving rush immunotherapy and 0–79% in patients receiving cluster immunotherapy [24, 26]. While rush immunotherapy is more risky than a conventional regimen [26], the frequency of systemic reactions with cluster schedules was similar to the rate of those with conventional schedules [19]. In a

double-blind study of cluster and conventional immunotherapy schedules with *D. pteronyssinus*, systemic adverse reactions with conventional schedules occurred in 4% of all patients (0.31% of all doses), compared with the similar frequency of systemic reactions with cluster schedules (3% of the patients and 0.15% of all doses). Meanwhile, it is generally accepted that premedication, such as antihistamines [27] or monoclonal anti-IgE antibody [28], reduces the risk of systemic reactions with rush immunotherapy [26]. However, its effects on either cluster or conventional schedules was not as clear [24]. In the present study, we observed mild systemic adverse reactions during the incremental-dose phase in 6.7% of the patients who received the cluster doses (1.0% of the injections) and in 6.8% of the patients who received the conventional doses (0.9% of the injections). The similar rates with premedication (antihistamine) indicated that our cluster schedule for the initial phase of immunotherapy with an incremental dose of *D. pteronyssinus* is a safe alternative to the conventional schedule, although we may not have clarified the effects of the antihistamine used before the injection. This needs to be investigated in a double-blind and placebo-controlled way. One of the concerns with the use of premedication is that it may mask milder systemic reactions, allowing serious reactions to occur in the build-up phase [27, 28]. However, our data indicated that the build-up phase and maintenance phase had similar rates of both local and systemic reactions, in both the cluster group and the conventional group.

Generally speaking, there was a continuous reduction in cutaneous sensitivity during the immunotherapy process [19, 29]. In the current study, we have seen similar reductions in cutaneous reactivity to *D. pteronyssinus* with both treatment schedules, although we have not compared the different kinetics of changes in skin sensitivity between the groups. These results were in line with the similar comparative data from Tabar et al. [19], which also indicated that cluster immunotherapy led to reduced cutaneous reactivity earlier than with the conventional schedule. Meanwhile, changes in specific IgE, which initially increases in the up-dosing phase and then decreases to basal levels a few months later [30], is not as consistent as other immunological markers, such as the IgG4 level [19]. After 1 year of treatment, we, together with others [19, 31, 32], have not recorded a significant change in levels of specific IgE in either cluster or conventional schedules.

In conclusion, our results showed that immunotherapy with a standardized extract of *D. pteronyssinus* in a 6-week cluster schedule was tolerated as well as a 14-week

conventional schedule. The cluster schedule had the advantages of saving time in reaching the maintenance dose and achieving clinical improvement sooner. Meanwhile, the cluster schedule produced a similar rate of systemic adverse reactions (all mild) when compared with the conventional schedule.

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