APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Safety of House Dust Mite Subcutaneous Immunotherapy with a rush and cluster combination protocol in the build-up phase

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Abstract

Background: Conventional and cluster subcutaneous immunotherapy (SCIT) are effective but may be time-consuming. Rush SCIT may offer a more convenient treatment option to patients and be of shorter duration; however, it is also associated with a higher incidence of systemic adverse reactions. Therefore, a combination of protocols between rush and cluster SCIT could have a superior risk-benefit ratio.

Objective: To determine the safety of the combination of rush and cluster HDM-SCIT and to identify the risk factors for local and systemic adverse reactions.

Methods: We retrospectively reviewed the charts of patients who received HDM-SCIT, with rush and cluster combination protocols, at a tertiary care hospital between January 2009 and December 2020. Data were collected at the initial visit (demographic data; underlying allergic disease; current medication; and laboratory investigation results including skin prick test, serum specific IgE (sIgE) levels to aeroallergen, total IgE, and eosinophil count) and follow-up visits (rate and severity of local and systemic adverse reactions).

Results: In total, 698 injections (28 patients) were reviewed. Overall, 13 patients developed systemic adverse reactions, at 3% (21/698) per injection visit. All reactions occurred within 60 minutes. In total, 6 patients experienced large local reactions, at 1.1% (8/698) per injection visit. A high level of sIgE to *D. pteronyssinus* was significantly associated with systemic adverse reactions (HR = 1.02; P = 0.009).

Conclusion: HDM-SCIT with a combination of rush and cluster schedules in the build-up phase could be used as an alternative protocol, given its acceptable systemic adverse reaction rate and shortened duration.

Key words: Allergen, Immunotherapy, House dust mites, Risk factor, Safety

Citation:
Yuenyongviwat, A., Jintanapanya, N., Sangsupawanich, P., Koosakulchai, V. Safety of House Dust Mite Subcutaneous Immunotherapy with a rush and cluster combination protocol in the build-up phase. *Asian Pac J Allergy Immunol.* https://doi.org/10.12932/ap-270822-1442

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Introduction

Subcutaneous immunotherapy (SCIT) is a highly effective therapy for allergic diseases, achieving long-term symptom remission.[1] SCIT is indicated for the treatment of severe allergic rhinitis, asthma, and venom anaphylaxis and is currently the only immune-modifying treatment for allergic diseases.[2,3] House dust mites (HDMs), particularly *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farina* (Df), are regarded as the most important indoor allergens causing allergic sensitization globally, especially in

tropical countries such as Thailand.[4,5] In addition, they lead to a number of allergic diseases such as allergic rhinitis, atopic asthma, and atopic dermatitis.[6,7] HDM-SCIT is beneficial to these patients.

The SCIT protocol consists of build-up and maintenance phases. The build-up phase divides the protocol into conventional and accelerated schedules.[8] Conventional immunotherapy generally consists of weekly or biweekly allergen injections, which are administered in gradually increasing doses until maintenance doses are reached at around 4 to 6 months, which is quite a long time. Further, this requires frequent hospital visits and possibly time away from school or work, resulting in treatment failure.[9] Accelerated build-up schedule involving cluster and rush build-up has been an alternative beneficial treatment method, which enables patients to rapidly achieve the maintenance dose. Cluster build-up usually includes 2–4 sequential injections per day on nonconsecutive days, allowing patients to reach the maintenance dose in 4–8 weeks. Rush build-up involves an increasing dose administered at intervals of 15–60 minutes over the course of 1–3 days until the maintenance dose is reached.[10] However, these methods are also associated with a greater risk of developing systemic responses.

Previous studies on HDM-SCIT have demonstrated that the incidence of systemic adverse reactions (SAEs) ranged from 0.31% to 4.6% per injection (3–20% of patients) for a conventional schedule, whereas this incidence is approximately 0.15–3.5% (7% of patients) for a cluster schedule and is higher at 4.2% per injections (27–35% of patients) for a rush schedule.[10-14]

A significant degree of skin test reactivity and a forced expiratory volume in one second (FEV_1) less than 80% of predicted were reported to be significant predictors of systemic reactions with rush immunotherapy to HDMs.[9] Higher body mass index (BMI) and serum specific IgE (sIgE) levels to HDMs are also reported as risk factors for developing local reactions (LRs).[15]

Therefore, combining rush and cluster protocols is preferable with respect to the risk-benefit ratio. However, the safety of this method against HDMs has not been thoroughly investigated. Hence, this study aimed to determine the safety of the combination of rush and cluster HDM-SCIT in the build-up phase and to identify risk factors for local and systemic adverse reactions.

Methods

Study design and study population

This was a retrospective chart review of patients who received HDM-SCIT with a rush and cluster combination protocol in the build-up phase at a tertiary care hospital; from January 2009 to December 2020. The eligibility criteria for HDM-SCIT were as follows: age > 5 years, treatment-resistant allergic disease, defined as patients with moderate-to-severe allergic rhinitis, moderate-to-severe allergic conjunctivitis, moderate-to-severe atopic dermatitis, and/or persistent asthma, that are not well tolerated with optimal avoidance measures and pharmacotherapy, sensitization to HDMs (sIgE level > 0.35 kUA/L), and $FEV_1 \geq 70\%$. Patients who did not complete the study protocol were excluded.

Data was collected from the medical records. Data on demographics (sex, age, underlying disease, onset of diagnosis, duration of treatment prior to receiving SCIT, and atopy comorbidity); total serum IgE level; serum eosinophil count; current medication; spirometry results; and aeroallergen serum sIgE levels to *D. pteronyssinus*, *D. farinae*, cockroach, bermuda, cat pelt, and dog pelt were collected at the initial visit. Follow-up data were also recorded, focusing on SAEs (onset and severity of the reaction) and large local reactions (LLRs). sIgE levels for aeroallergens were assessed using ImmunoCap. Sensitization to aeroallergens was defined as a sIgE level > 0.35 kUA/L.

Allergen extract and rush and cluster combination protocol

HDM-SCIT was performed using an HDM preparation (ALK-Abello, Port Washington, NY, USA) containing a 50:50 mixture of *D. pteronyssinus* and *D. farinae* extracts. The HDM extract used for maintenance immunotherapy was 500 AU (0.5 mL/dose), which was a mixture of the 250 AU/each allergen extracts.

As part of the HDM-SCIT rush protocol, all patients were admitted to the hospital for 3 days (three injections per day for three consecutive days) and were administered prednisolone (1 mg/kg/day, max 40 mg) and an antihistamine (cetirizine 5 mg or loratadine 5 mg) 1 hour before the first injection. Subsequently, they visited the allergy clinic once weekly for the HDM-SCIT cluster protocol, in which the patient received two injections each day. Accordingly, the rush and cluster combination protocol consisted of 7 weeks and 21 injections (**Table 1**). A physician, nurse practitioner, or physician assistant was present during immunotherapy administration and during the observation period. Patients were observed for 30 minutes between the doses and after the final dose of the day.

Table 1. Rush and cluster combination protocol.

			Concentration of allergen extract	Volume (mL)
Rush schedule	Week 1	Day 1	1:1000	0.1
			1:1000	0.2
			1:1000	0.4
		Day 2	1:100	0.1
			1:100	0.3
			1:100	0.5
		Day 3	1:10	0.1
			1:10	0.2
			1:10	0.3

Table 1. (Continued)

		Concentration of allergen extract	Volume (mL)
Cluster schedule	Week 2	1:10	0.35
		1:10	0.4
	Week 3	1:10	0.5
		1:1	0.1
	Week 4	1:1	0.15
		1:1	0.2
	Week 5	1:1	0.25
		1:1	0.3
	Week 6	1:1	0.35
		1:1	0.4
	Week 7	1:1	0.45
		1:1	0.5

Evaluation of reactions

All systemic reactions were assessed based on the World Allergy Organization Subcutaneous Immunology Systemic Reaction Grading System. Large local reactions (LLRs) were assessed according to the size of the local swelling (wheal), and those with a mean diameter of 25 mm were considered LLRs.[3]

Sample size calculations

We calculated the sample size for the detected rate of systemic adverse reaction of HDM-SCIT in the built-up phase, using a formula for estimating the infinite population proportion (P; rate of adverse reaction in rush protocol = 0.04).[10] The overall sample size was calculated as 60 injections.

Statistical analysis

Demographic data are presented as the mean ± standard deviation or median for continuous data and as number (%) for categorical data. The number and severity of systemic and local adverse reactions, systemic reaction rate per injection visit, and local reaction rate per the number of injections were determined. Cox regression analysis was used for univariate and multivariate analyses. Variables, including baseline characteristics and laboratory findings, were used to estimate the risk factors associated with systemic reactions. All statistical analyses were performed using a standard software package (Stata version 13.0; StataCorp). $P < 0.05$ was considered significant.

Ethics statement

This study was approved by the Ethics Committee and Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (IRB number is 64-118-01-1).

Results

Patient characteristics

A total of 28 patients (698 injections) who underwent rush and cluster combination subcutaneous immunotherapy for HDM were evaluated (**Table 2**). The mean age was 14.7 years, and 16 children (57.1%) were male. The most common diseases indicated for HDM-SCIT were atopic dermatitis (35.7%), asthma (32.1%) and allergic rhinitis (25%), and allergic rhinitis (81.8%) was the most common comorbidity. The median sIgE to *D. pteronyssinus* was 73 kU/L, and the mean sIgE to *D. farinae*, 48.6 kU/L. The mean FEV_1 was 92%, and 46% of patients received more than 400 mcg of inhaled corticosteroid once daily. The mean serum total IgE level was 2,010.2 kU/L, and the mean eosinophil count was 563.3 mm^3.

Table 2. Baseline characteristics.

Characteristic	Total (N = 28)
Age (years), median (IQR)	14.7 (12.6,16)
Sex (male), n (%)	16 (57.1)
Diseases that are indicated for immunotherapy, n (%)	
Asthma	9 (32.1)
Allergic rhinitis	7 (25.0)
Atopic dermatitis	10 (35.7)
Severe allergic conjunctivitis	1 (3.6)
Chronic spontaneous urticaria	1 (3.6)
Comorbid of allergic diseases, n (%)	22 (78.6)
Asthma	5 (22.7)
Allergic rhinitis	18 (81.8)
Atopic dermatitis	3 (13.6)
Allergic conjunctivitis	1 (4.5)
Onset of diagnosis (month), median (IQR)	97.4 (67.6-132.1)
Duration of treatment (month), median (IQR)	34.5 (14.9-54.7)
Specific serum IgE, kU/L (%)	
Dermatophagoides. pteronyssinus, median (IQR)	73 (19.5, 100)
Dermatophagoides farinae, mean (SD)	48.6 (42)
Cockroach, median (IQR)	3.3 (13.1)
Cat pelt, mean (SD)	11.4 (29.2)
Bermuda, mean (SD)	2.6 (10)
Dog pelt, mean (SD)	0.3 (0.3)
Pulmonary function test, mean (SD)	
FVC	95.7 (10.7)
FEV_1	92 (16.5)
FEV_1/FVC	96.7 (9.9)
$FER_{25-75\%}$	83 (19.3)
PEFR	84.7 (19.6)

Table 2. Baseline characteristics.

Characteristic	Total (N = 28)
Total IgE (kU/L), mean (SD)	2,010.2 (2,567.7)
Eosinophil number (mm^3), mean (SD)	536.3 (573)
Omalizumab, n (%)	4 (14)
Daily dose of inhaled corticosteroid, n (%)	13 (46.4)
0-200	1 (7.7)
200-400	6 (46.2)
> 400	6 (46.2)
Daily dose of intranasal corticosteroid, n (%)	25 (89.3)
0-50	5 (20)
50-100	14 (56)
> 100	6 (24)

Abbreviation: IQR, interquartile range; SD, standard deviation; FEV_1, forced expiration in 1 second; FVC, Forced Vital Capacity; $FEF_{25-75\%}$, forced expiratory flow at 25 – 75% of FVC, PEFR, Peak expiratory flow rate

Incidence and severity of adverse reactions

In total, 13 patients developed systemic adverse reactions, 3% (21/698) per injection. Among them, 6 patients developed LLRs, 1.1% (8/698) per injection. The most common adverse reactions were grade II systemic reactions (1.4%). The incidence of systemic adverse reactions was higher in the rush schedule (2.3%); grade I systemic reactions occurred in 1.1%. LLRs were also more common in the rush schedule than in the cluster schedule (0.9% vs 0.3%) (**Table 3**). Almost all systemic reactions occurred within the first 60 minutes of injection. The characteristics, including prescribed medication of the patients who developed systemic adverse reactions, are shown in **Table 4**.

Risk factors associated with SAEs and LLRs

Univariate analysis showed that serum sIgE to Dp was significantly associated with the development of SAEs (HR = 1.01; $P = 0.02$). Meanwhile, age and serum sIgE to cockroaches were significantly associated with decreased SAEs with HR = 0.93; $P = 0.03$ and HR = 0.39; $P = 0.04$, respectively. FEV_1 and receiving omalizumab decreased the incidence of SAEs; however, this difference was insignificant. In terms of LLRs, univariate analysis revealed that serum sIgE to Df was significantly associated with LLRs (HR = 1.02; $P = 0.04$) (**Table 5**).

Table 3. Reactions from combination rush and cluster HDM-SCIT protocol.

Reaction grade	Number of overall reactions (N = 698)	Number of reactions classified by schedule of build-up phase	
		Rush schedule	Cluster schedule
Systemic reaction, n (%)	21 (3.0)	16 (2.3)	5 (0.7)
Grade 1, n (%)	8 (1.1)	8 (1.1)	0 (0)
Grade 2, n (%)	10 (1.4)	5 (0.7)	5 (0.7)
Grade 3, n (%)	3 (0.4)	3 (0.4)	0 (0)
LLR, n (%)	8 (1.1)	6 (0.9)	2 (0.3)

Abbreviation: LLR, large local reaction

Table 4. Type, severity, and timing of systemic reaction during combination rush and cluster HDM-SCIT protocol.

No	Dose of HDM-SCIT				Detail of systemic adverse reaction		Treatment
	Schedule	Concentration of allergen extract	Volume (mL)	Onset (minutes)	Severity grade of systemic reaction	Clinical presentation	
1	Rush	1:100	0.5	30	3	Generalized urticaria, expiratory wheezing	Adrenaline, CPM, hydrocorticosteroid
2	Rush	1:10	0.2	60	3	Generalized urticaria, angioedema, wheezing	Adrenaline, CPM, hydrocorticosteroid
3	Rush	1:100	0.3	60	1	Generalized urticaria	CPM
4	Rush	1:10	0.3	30	2	Generalized urticaria	CPM
5	Rush	1:10	0.2	25	2	Generalized urticaria, expiratory wheezing	Adrenaline, CPM, hydrocorticosteroid, Ventolin

Table 4. (Continued)

No	Dose of HDM-SCIT				Detail of systemic adverse reaction		Treatment
	Schedule	Concentration of allergen extract	Volume (mL)	Onset (minutes)	Severity grade of systemic reaction	Clinical presentation	
6	Cluster	1:1	0.1	40	2	Expiratory wheezing	Ventolin, Prednisolone
7	Rush	1:100	0.5	30	1	Generalized urticaria	CPM
8	Rush	1:10	0.5	20	1	Generalized urticaria	Cetirizine
9	Rush	1:100	0.5	40	2	Expiratory wheezing, itching	CPM, Ventolin
10	Rush	1:1000	0.1	30	1	Rhinorrhea, nasal congestion	Cetirizine
11	Rush	1:100	0.5	30	1	Generalized urticaria	CPM
12	Rush	1:10	0.2	30	2	Generalized urticaria, expiratory wheezing	Adrenaline, CPM, hydrocorticosteroid, Ventolin
13	Rush	1:10	0.25	30	1	Generalized urticaria	CPM
14	Cluster	1:1	0.3	30	2	Cough, nasal congestion, expiratory wheezing	Ventolin
15	Rush	1:100	0.5	90	1	Generalized urticaria, chest tightness, cough	CPM
16	Cluster	1:1	0.2	180	2	Local urticaria, chest tightness	Cetirizine, Ventolin
17	Cluster	1:1	0.2	120	2	Expiratory wheezing, nasal congestion	Ventolin, Prednisolone
18	Cluster	1:1	0.5	240	2	Local urticaria, chest tightness	Cetirizine, Ventolin
19	Rush	1:10	0.3	60	3	Cough, nasal congestion, expiratory wheezing	Adrenaline, CPM, hydrocorticosteroid, Ventolin
20	Rush	1:10	0.2	60	1	Generalized urticaria, nasal congestion	Adrenaline, CPM, hydrocorticosteroid
21	Rush	1:10	0.2	60	2	Generalized urticaria, nasal congestion, chest tightness	Adrenaline, CPM, hydrocorticosteroid

Table 5. Univariate analysis for risk factors associated with systemic and large local reactions.

Factors	SAEs			LLRs		
	HR	95%CI	*p* Value	HR	95%CI	*p* Value
Age (years)	0.93	0.87-0.99	**0.03**	1.05	0.98-1.12	0.19
Sex (male)	1.27	0.40-4.04	0.68	0.45	0.09-2.19	0.32
Asthma	1.13	0.28-4.54	0.87	3.11	0.30-32.20	0.34
Degree of skin test to Dp	1.05	0.84-0.30	0.64	1.23	0.37-4.16	0.74
Degree of skin test to Df	1.15	0.88-1.52	0.30	1.12	0.57-2.19	0.75
sIgE to Dp	1.01	1.00-1.03	**0.02**	1.01	0.99-1.03	0.18
sIgE to Df	1.00	0.99-1.02	0.76	1.02	1.00-1.04	**0.04**
sIgE to Cockroach	0.39	0.16-0.94	**0.04**	0.98	0.95-1.02	0.37
FEV_1	0.96	0.92-1.01	0.10	0.94	0.86-1.02	0.14
Omalizumab	0.49	0.08-3.10	0.45	3.00	0.85-15.64	0.19

Abbreviation: HR, hazard ratio; SAEs, systemic adverse reactions; LLRs, large local reactions; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farina*; sIgE, Specific IgE; FEV_1, forced expiration in 1 second.

Table 6. Multivariate analysis for risk factors associated with systemic and large local reactions.

Factors	SAEs			LLRs		
	HR	95%CI	*p* Value	HR	95%CI	*p* Value
Age (years)	0.96	0.89 - 1.02	0.19	1.04	0.99 - 1.09	0.08
Sex (male)	1.43	0.61 - 3.37	0.42	1.62	0.37 - 7.04	0.52
sIgE to Dp	1.02	1.01 - 1.03	**0.009**			
sIgE to Df				1.02	1.00 - 1.03	**0.02**
sIgE to Cockroach	0.29	0.58 - 1.53	0.15			

Abbreviation: HR, hazard ratio; SAEs, systemic adverse reactions; LRs, large local reactions; sIgE, Specific IgE.; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farina;*

Multivariable analysis revealed that only serum sIgE to Dp was significantly associated with the development of SAEs (HR = 1.02; 95%CI: 1.01-1.03, P = 0.009), while serum sIgE to Df (kU/L) was only significantly associated with the development of LLR. (HR = 1.02; 95%CI: 1.00-1.03, P = 0.25) (**Table 6**).

Other factors such as age, asthma, allergic rhinitis, degree of skin test reactivity, mean serum total IgE level, the mean eosinophil count, and dose of inhaled corticosteroid in asthmatic patients were not associated with the development of SAEs or LLRs.

Discussion

The safety of a combination of cluster and rush protocols in the build-up phase for HDM-SCIT is yet to be clarified. In this study, the rate of systemic reactions was 3% per injection visit. Most of the adverse systemic reactions were mild to moderate and occurred within 60 minutes. Furthermore, the rate of LLR was 1.1% per injection visit.

A recent systematic review showed that systemic reactions occur in 0.05-3.2% and 0.15-3.3% per injection for conventional and cluster aeroallergen immunotherapy, respectively.[9] In terms of systemic reactions to HDM-SCIT, previous studies have reported that its incidence ranged from 0.31% to 4.6% and from 0.15% to 3.5% per injection for conventional and cluster schedules, respectively. However, this incidence was greater for rush schedules, reaching 4.2% per injection. This study's systemic reactions rate is consistent with those reported for the conventional and cluster technique.[10-14] Moreover, the combination protocol has the advantage of a reduced number of clinic visits, saving the patient time and reducing costs, ultimately increasing the convenience of this treatment.

The rates of systemic reactions in rush immunotherapy (RIT) range from 27% to 100% for patients treated with RIT without premedication and from 7.2% to 27% for patients treated with premedication.[16-18] This indicates that premedication decreases the reaction rate. Many previous studies showed that pretreatment with second-generation antihistamines could reduce the rates of SAEs for accelerated build-up schedules.[19-21] Moreover, some studies found that omalizumab significantly reduced the rate of SAEs to rush immunotherapy.[22,23] In this study, all patients were administered antihistamine 1 hour before injection, and 14% received omalizumab. However, we did not find any significant association between omalizumab and SAEs, possibly because of the small number of patients with asthma diagnoses and the exclusions of people who had FEV_1 less than 70%. In this study, higher systemic reactions occurred during the rush period, indicating that care should be taken during this period. However, most systemic reactions were only of mild to moderate severity (grades 1-3). The patient's symptoms improved with medication, as shown in **Table 4**, and there was no need for intensive unit care; no patient died. Our findings support that patients should be hospitalized during the rush period for close monitoring and premedication before HDM-SCIT injection to reduce the risk of systemic adverse reactions.

One of the main reasons for poor SCIT adherence is the inconvenience of coming to the clinic to receive allergy injections, especially in the build-up phase.[24,25] Therefore, it has been suggested that shortening the treatment schedules by reducing the number of injections could indirectly improve the adherence rate.[26] Compared to other cluster protocols, our protocol helps decrease the cluster period time as we had previously implemented a rush schedule. Accordingly, combining cluster and rush schedules in the build-up phase of the HDM-SCIT protocol can balance the risks and benefits of treatment.

Our results showed that a high level of sIgE to Dp was significantly associated with SAEs, and a high level of sIgE to Df was significantly associated with LLRs. This finding suggests that a high level of HDM sensitization may be associated with systemic reactions to SCIT, in accordance with the findings of other studies that have demonstrated the degree of skin test reactivity as a predictor of systemic reactions during immunotherapy. DaVeiga et al showed that 3-4+ positive skin tests are associated with systemic reactions in aeroallergen immunotherapy (OR: 5.8, 95%CI: 1.2-27.6).[27] Parmiani et al also found an association between the degree of skin test results and systemic reactions in inhalant SCIT.[28]

There are a number of limitations mentioned in this study. First, since this study is a single-center observational retrospective study and had a small patient population, additional clinical studies involving HDM-SCIT patients with a larger patient population might be required to confirm the safety of the rush and cluster combination protocol. Second, as prednisolone and an antihistamine were administered to

all patients as premedication, this study is unable to assess whether premedication has any effect on reducing SAEs. In addition, regarding the exclusion of patients with FEV_1 less than 70% in this study, it may have an impact on the assessment of the association between omalizumab and SAEs.

Conclusion

HDM-SCIT with a combination of rush and cluster schedules in the build-up phase showed an acceptable systemic adverse reaction rate and shortened duration, indicating that it could be used as an alternative protocol.

Acknowledgments

The authors gratefully acknowledge all of the Epidemiology staff from the Faculty of Medicine, Prince of Songkla University, for assistance in the data analysis.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Source of funding

This was an unfunded study.

Authors' contributions

- AY, VK designed the study, performed the analysis and manuscript preparation.
- NJ designed the study and performed the data collection.
- PS designed the study and performed the analysis.
- All authors have read and approved the final manuscript.

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