Asia Pac Allergy. 2021 Jul;11(3):e32
https://doi.org/10.5415/apallergy.2021.11.e32
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Original Article

Clinical evaluation of rush immunotherapy using house dust mite allergen in Japanese asthmatics

Takahiro Uchida, Kazuyuki Nakagome*, Hidetoshi Iemura, Erika Naito, Sachiko Miyauchi, Yoshitaka Uchida, Tomoyuki Soma, and Makoto Nagata

Department of Respiratory Medicine and Allergy Center, Saitama Medical University, Saitama, Japan

Received: Jan 31, 2021
Accepted: Jul 8, 2021

***Correspondence to**
Kazuyuki Nakagome
Department of Respiratory Medicine and Allergy Center, Saitama Medical University, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.
Tel: +81-49-276-1319
Fax: +81-49-276-1319
Email: nakagomek-tky@umin.ac.jp

ORCID iDs
Takahiro Uchida
https://orcid.org/0000-0002-8697-8557
Kazuyuki Nakagome
https://orcid.org/0000-0003-3138-1451
Hidetoshi Iemura
https://orcid.org/0000-0003-2712-1673
Erika Naito
https://orcid.org/0000-0001-7757-7199
Sachiko Miyauchi
https://orcid.org/0000-0002-0689-9622
Yoshitaka Uchida
https://orcid.org/0000-0001-8562-707X
Tomoyuki Soma
https://orcid.org/0000-0001-7492-9515
Makoto Nagata
https://orcid.org/0000-0001-7686-5826

ABSTRACT

Background: Allergen immunotherapy (AIT) is a specific treatment of administering clinically important allergens to patients who have allergic diseases. In Japan, the standardized house dust mite (HDM) allergen for subcutaneous immunotherapy (SCIT) was approved in 2015, and we then introduced rush-immunotherapy (rush-IT) using the standardized HDM allergen for HDM-sensitive asthmatics. However, little data are available on the safety and effectiveness of rush-HDM-IT, especially for Japanese asthmatics.
Objective: The objective of this study was to examine the safety and clinical effectiveness of rush-IT using the standardized HDM for HDM-sensitive Japanese asthmatics.
Methods: Thirteen HDM-sensitive asthmatics who received rush-HDM-IT and 12 HDM-sensitive asthmatic controls were enrolled. To evaluate the safety, the number of systemic reaction (SR) events, including anaphylaxis, was assessed. To evaluate the effectiveness, changes in the treatment step, dose of inhaled corticosteroid, and asthma control after rush-HDM-IT and the subsequent maintenance SCIT were assessed. Changes in the HDM-induced production of type 2 cytokines from peripheral blood mononuclear cells were also evaluated.
Results: Among the 12 patients who received rush-IT, 4 (30.7%) experienced a SR and 3 (23.1%) experienced anaphylaxis. However, the anaphylaxis was not severe (grade 3) in all cases, and they recovered in a short time. The treatment step of asthma was better and the dose of inhaled corticosteroid was lower in the rush-HDM-IT group than in the control group. The HDM-induced production of both interleukin (IL)-5 and IL-13 from peripheral blood mononuclear cells was significantly lower in the rush-HDM-IT group than in the control group.
Conclusion: Rush-HDM-IT can be performed relatively safely in Japanese asthmatics. Furthermore, rush-HDM-IT and the subsequent maintenance SCIT provided clinical improvement in asthma patients, and was accompanied by the suppression of HDM-specific Th2-mediated systemic immune responses.

Keywords: Allergen immunotherapy; Bronchial asthma; House dust mite; Rush immunotherapy; Subcutaneous immunotherapy

Conflict of Interest

MN received fees for speaking from Torii Pharmaceutical Co., Ltd. The rest of the authors declare no conflicts of interest.

Author Contributions

Conceptualization: Kazuyuki Nakagome, Makoto Nagata. Formal analysis: Takahiro Uchida, Kazuyuki Nakagome. Investigation: Takahiro Uchida, Hidetoshi Iemura, Erika Naito, Sachiko Miyauchi, Yoshitaka Uchida, Tomoyuki Soma. Methodology: Takahiro Uchida, Kazuyuki Nakagome, Tomoyuki Soma. Project administration: Kazuyuki Nakagome, Makoto Nagata. Writing - original draft: Takahiro Uchida, Kazuyuki Nakagome. Writing - review & editing: Kazuyuki Nakagome, Makoto Nagata.

INTRODUCTION

Allergen immunotherapy (AIT) is a treatment of administering increasing doses of clinically important allergens to patients who have allergic diseases [1, 2]. The efficacy of treatment by AIT has already been established in allergic asthma, allergic rhinitis, and hymenoptera hypersensitivity [1-3]. In addition, AIT is the only existing treatment that can modify the pathological immune response underlying the allergic disease [1, 2]. AIT includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SCIT is a treatment in which allergens are injected subcutaneously, whereas SLIT is a treatment in which allergens are placed sublingually for several minutes before being swallowed.

House dust mite (HDM) is a globally important allergen that causes allergic rhinitis and bronchial asthma [4]. However, standardized HDM allergens for SCIT were not available in Japan. Before 2015, house dust collected from ordinary Japanese households had been used as an alternative allergen product for AIT. The major active component of house dust obtained from Japanese residences was mites, but there were product quality issues, and it was necessary to improve the effectiveness and safety of the allergen by adopting a standardized HDM allergen. A standardized purified HDM allergen for SCIT was officially approved in Japan in 2015, and it is presently still being used for the treatment of asthma. However, little data are available on the safety and effectiveness of SCIT for asthma using the standardized purified HDM allergen in Japanese populations.

In conventional SCIT, hospital visits 1 or 2 times a week are required for several months during the initial build-up phase, and since it can be inconvenient for some patients, adherence to this schedule is an important challenge for SCIT in patients with allergic diseases [5-7]. To dissolve this issue, rush schedule of SCIT has been developed to reduce the treatment schedule, especially to reduce patient effort during the build-up phase. In the rush schedule of SCIT, the build-up phase is usually completed in 5 to 7 days [5-7]. However, the incidence of systemic reaction (SR) events is higher in rush-SCIT than in conventional SCIT [5-12]. We recently introduced rush-HDM immunotherapy (IT) to patients with HDM-sensitive asthma who were admitted to our hospital for the monitoring of the development of a SR. In this study, we investigated the safety and clinical effectiveness of rush-IT using the standardized HDM for asthma in this study. The effect of rush-IT on the production of type 2 cytokines from peripheral blood mononuclear cells (PBMCs) was also evaluated.

MATERIALS AND METHODS

Patients

Patients with HDM-sensitive bronchial asthma who had an indication for HDM-SCIT and agreed to receive rush-HDM-IT were recruited from the Allergy Center of Saitama Medical University to this study from August 2015 to December 2018. An indication for HDM-SCIT in atopic asthma was defined as mild-to-moderate persistent asthma with a percent predicted forced expiratory volume in 1 second (%FEV_1) of ≥70% [1, 2]. Patients with HDM-sensitive bronchial asthma who did not agree to receive AIT were recruited as controls. In both groups, the standard asthma treatment based on the Japanese guideline (JGL) [13] had already been performed before the patients were enrolled into this study. Asthma was diagnosed according to the definition of the Global Initiative for Asthma guidelines: the presence of asthmatic symptoms, exacerbation and wheezing, and bronchial reversibility that responded to

bronchodilators and/or bronchial hyperresponsiveness to methacholine challenge [14]. The study was approved by the Institutional Review Board of Saitama Medical University Hospital (approval number: 14-008). Written informed consent was obtained from all individuals.

Rush-HDM-IT

Rush-IT was conducted as described previously [15, 16]. Each patient in the rush-HDM-IT group was hospitalized and received subcutaneous injections of the standardized purified HDM extract (*Dermatophagoides farinae*/*Dermatophagoides pteronyssinus*; Torii Pharmaceutical Co., Ltd., Tokyo, Japan). To prevent a SR or local reaction, the following medications were administered during rush-IT in addition to antiasthma drugs: 3 mg of oral mequitazine twice or 3 times daily, and the inhalation of both 20 mg of disodium cromoglycate and 2.5 mg of salbutamol hemisulfate 4 times daily [15, 16]. The initial concentration of the injection was diluted to 1/10 of the threshold concentration determined by skin test titration. Each subject received 2 to 4 subcutaneous shots daily at 2-hour intervals for 5 days (**Supplementary material 1**). If the diameter of the erythema became larger than 50 mm, the same dose was used again. The final dose was set at 0.3 mL of 1,000 JAU/mL (300 JAU) unless a SR was provoked. When a SR, such as an asthmatic symptom, appeared, the patient was carefully examined and promptly given appropriate therapy; thereafter, the dose of the next injection was reduced to one-half of the dose of the SR-inducing injection. After confirming the safety of that dose, it was used as the maintenance dose. After discharge, injection of the maintenance dose was repeated every 2 weeks in the outpatient clinic, then the interval was eventually extended to every 4 weeks.

Safety

The number of SR and anaphylaxis events in the build-up phase of rush-HDM-IT and the maintenance phase of SCIT was evaluated. SR and anaphylaxis events were graded according to the systemic allergic reaction grading system of the World Allergy Organization (WAO) [17]. Grades 1 and 2 are designated as SR events, and grades 3 to 5 are designated as anaphylaxis events [17]. We also recorded the types of symptoms that occurred as the SR or anaphylaxis events in this study.

Effectiveness

The clinical effectiveness of rush-HDM-IT and maintenance SCIT for asthma was evaluated by the changes in treatment step according to the JGL [13], and the changes in the dosage of inhaled corticosteroid (ICS) at the following time points: before rush-HDM-IT induction, 1 year after rush-IT, and 2 years after rush-IT. We also evaluated the rates of patients who could receive step-down asthma treatment. In addition, we evaluated the asthma control status using the Asthma Control Test (ACT) score, Asthma Control Questionnaire (ACQ) score, and the visual analogue scale (VAS) for asthma control in the Self-Assessment of Allergic Rhinitis and Asthma (SACRA) questionnaire (SACRA A-VAS) [18]. We also assessed the rhinitis control status using a VAS for rhinitis control in the SACRA questionnaire (SACRA R-VAS) [18].

To investigate potential biomarkers for the effectiveness of rush-HDM-IT and the subsequent maintenance SCIT, we measured the fractional exhaled nitric oxide (FeNO), blood eosinophil counts, and the HDM-specific IgE/total IgE in serum before rush-IT. We also measured some of these biomarkers during maintenance SCIT (1 or 2 years after rush-IT).

Peripheral blood mononuclear cells

PBMCs from the rush-HDM-IT group were obtained before rush-HDM-IT induction and during the maintenance period (1 year after rush-IT), as described previously [16, 19, 20]. PBMCs from

the control group were also obtained at the same time. The PBMCs were incubated *in vitro* for 4 days in the presence of 1 μg/mL of *Dermatophagoides farinae* (*Df*; Torii Pharmaceutical Co., Ltd.) [21], a HDM, and the cytokine concentrations of the supernatant were measured using Bio-Plex human cytokine assay kits (Bio-Rad, Mississauga, ON, Canada).

Statistical analysis

Univariate analysis was performed using the chi-square test, the Student *t* test, and the Mann-Whitney *U* test with GraphPad Prism ver. 9 (GraphPad Software Inc., La Jolla, CA, USA) software. As for matched-pair data, we used a paired *t* test if the distribution of data was normal, or the Wilcoxon signed-rank test if the distribution of data was not normal.

RESULTS

Characteristics of the patients

Table 1 shows the characteristics of the rush-HDM-IT group and the control group. HDM-sensitized asthmatic patients who received guideline-based asthma treatment and further received rush-HDM-IT and subsequent maintenance SCIT for more than 2 years were enrolled into the rush-HDM-IT group. HDM-sensitized asthmatic patients who received guideline-based asthma treatment, but did not receive rush-HDM-IT despite the indication for HDM-IT were enrolled into the control group. There was no significant difference in sex distribution, smoking history, treatment step of bronchial asthma as assessed by JGL, ACT score, ACQ score, SACRA A-VAS, or SACRA R-VAS between the 2 groups. However, the average age of the control group (45.0 years) was significantly higher than that of the rush-HDM-IT group (30.9 years, $p < 0.05$). In the rush-HDM-IT group, 9 out of 13 patients also received concurrent rush-IT using Japanese cedar pollen (JCP) allergen as well as maintenance JCP-SCIT.

Safety

Table 2 shows the safety profile of rush-HDM-IT and maintenance SCIT in the patients enrolled into this study. In total, 4 patients (30.7%) showed a SR and 3 patients (23.1%) showed

Table 1. Characteristics of the patients

Characteristic	Rush-HDM-IT (N = 13)	Control (N = 12)	*p* value
Age (yr)	30.9 (18–52)	45 (26–71)	0.013
Sex, male:female	5:8	3:9	NS
Smoking history, yes:no	2:11	2:10	NS
Asthma treatment step (JGL), 1:2:3:4	1:7:4:1	1:8:4:0	NS
ACT	18.9 (12–25)	23.9 (21–25)	NS
ACQ	0.7 (0–2.4)	0.3 (0–1.0)	NS
SACRA A-VAS	2.4 (0–10)	1.0 (0–7)	NS
SACRA R-VAS	3.1 (0–8)	1.8 (0–7)	NS

Values are presented as mean (range) or number.
HDM-IT, house dust mite-immunotherapy; Asthma treatment step (JGL), bronchial asthma treatment step defined in the Japanese guideline issued by the Japanese Society of Allergology; ACT, Asthma Control Test; ACQ, asthma control questionnaire; SACRA A-VAS, VAS for asthma control in the SACRA questionnaire; SACRA R-VAS, VAS for allergic rhinitis in the SACRA questionnaire; VAS, visual analogue scale.

Table 2. Occurrence of systemic reaction and anaphylaxis events

Variable	Rush phase		Maintenance phase		Total	
	Patients (N = 13)	Injections (N = 207)	Patients (N = 13)	Injections (N = 502)	Patients (N = 13)	Injections (N = 709)
Systemic reaction	4 (30.7)	5 (2.4)	2 (15.3)	2 (0.4)	4 (30.7)	7 (1.0)
Anaphylaxis	3 (23.1)	3 (1.4)	0 (0)	0 (0)	3 (23.1)	3 (0.4)

Values are presented as number (%).

https://doi.org/10.5415/apallergy.2021.11.e32

anaphylaxis. All cases of anaphylaxis occurred after >100 JAU (0.1 mL of 1,000 JAU/mL) of HDM allergen was injected; however, none were severe (grade 3 in the WAO systemic allergic reaction grading system), and they all recovered within a short time. Out of the total 709 injections, a SR occurred 7 times (1.0%) and anaphylaxis occurred 3 times (0.4%). In the build-up phase, 4 patients (30.7%) experienced a SR and 3 patients (23.1%) experienced anaphylaxis; out of the total 207 injections in the build-up phase, a SR occurred 5 times (2.4%) and anaphylaxis occurred 3 times (1.4%). All patients who had a SR or anaphylaxis event in this study experienced the same event in the build-up phase. In the maintenance phase, 2 patients (15.3%) experienced a SR and no patients experienced anaphylaxis; out of the total 502 injections in the maintenance phase, a SR occurred 2 times (0.4%) and anaphylaxis occurred 0 times. Among the SR events, skin symptoms or findings were observed in 6 cases, respiratory symptoms or findings were observed in 6 cases, and digestive symptoms or findings were observed in 2 cases; all recovered within a short time.

Effectiveness

The clinical effectiveness of rush-HDM-IT and maintenance SCIT for asthma was evaluated by the changes in treatment step or in the maintenance dose of ICS for up to 2 years. The treatment step at 2 years after rush-IT was significantly lower in the rush-HDM-IT group than in the control group (Rush-HDM-IT vs. control: 1.8 vs. 2.4, $p = 0.004$; **Fig. 1A**). Furthermore, the ICS dose at 2 years after rush-IT was also lower in the rush-HDM-IT group than in the control group (Rush-HDM-IT vs. control: 57.8% vs. 120.8%, $p = 0.039$; **Fig. 1B**). The rate of patients who could receive step-down asthma treatment at 1 and 2 years after rush-IT was significantly higher in the rush-HDM-IT group than in the control group (Rush-HDM-IT vs. control, after 1 year: 46.1% vs. 8.3%, $p = 0.035$; after 2 years: 61.5% vs. 8.3%, $p = 0.006$; **Table 3**).

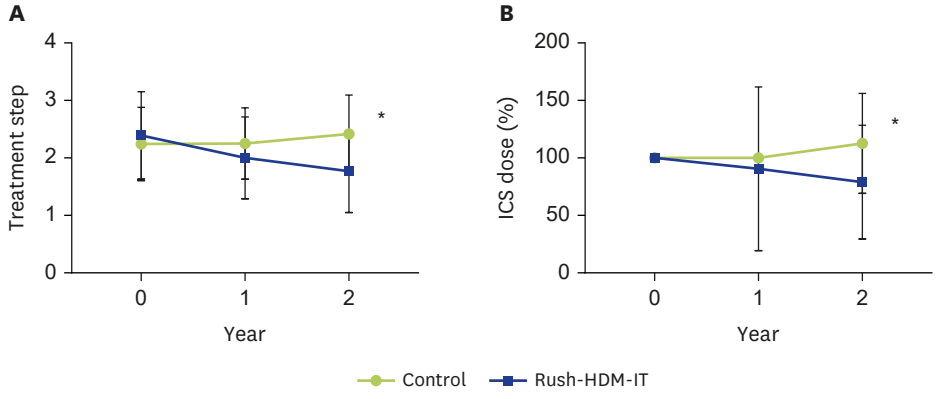

Fig. 1. Changes in the treatment step of asthma or dose of ICS after rush-HDM-IT and the subsequent maintenance subcutaneous immunotherapy. (A) Treatment step. The treatment step of bronchial asthma was determined based on the Japanese guideline. (B) ICS dose. The ICS dose before the induction of rush-IT or at a similar time point (year 0) was used as a control (100%). *$p < 0.05$ when compared with Rush-HDM-IT. ICS, inhaled corticosteroid; HDM-IT, house dust mite-immunotherapy.

Table 3. Rates of patients who could receive step-down treatment

	Rush-HDM-IT (N = 13)	Control (N = 12)	*p* value
After 1 year	6/13 (46.1)	1/12 (8.3)	0.035
After 2 years	8/13 (61.5)	1/12 (8.3)	0.006

Values are presented as number (%).
HDM-IT, house dust mite-immunotherapy.

https://doi.org/10.5415/apallergy.2021.11.e32

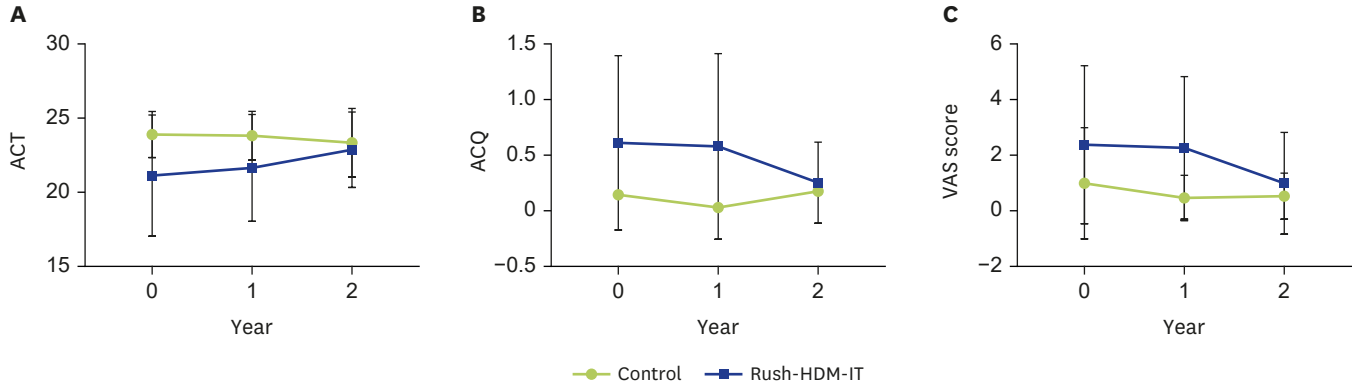

Fig. 2. Changes in asthma control after rush-HDM-IT and the subsequent maintenance subcutaneous immunotherapy. (A) ACT, (B) ACQ, and (C) VAS for asthma control in the Self-Assessment of Allergic Rhinitis and Asthma questionnaire. HDM-IT, house dust mite-immunotherapy; ACT, Asthma Control Test; ACQ, asthma control questionnaire; VAS, visual analogue scale.

Symptom scores

The ACT score, ACQ score, SACRA A-VAS, and SACRA R-VAS were evaluated. The ACT score tended to increase after rush-HDM-IT and maintenance SCIT, however, the difference was not statistically significant ($p > 0.05$) (**Fig. 2A**). The ACQ score tended to decrease after rush-HDM-IT and maintenance SCIT, however, the difference was not significant ($p > 0.05$) (**Fig. 2B**). Finally, the SACRA A-VAS and SACRA R-VAS tended to decrease after rush-HDM-IT and maintenance SCIT, however the differences were not significant ($p > 0.05$ for both; **Fig. 2C** and data not shown, respectively).

Predictive biomarkers for the effectiveness in asthma

We next examined potential biomarkers for the effectiveness of rush-HDM-IT and maintenance SCIT in asthma. We divided the patients who received rush-HDM-IT and maintenance SCIT into 2 groups, a step-down-achieved group and a step-down-not-achieved group, and compared the values of the FeNO, blood eosinophil count, and HDM-specific IgE/total IgE in serum before the induction of rush-HDM-IT between the 2 groups. The FeNO before rush-IT induction showed no association with the effectiveness of rush-HDM-IT for asthma at 2 years after rush-IT (step-down-achieved group vs. step-down-not-achieved group: 27.8 ppb vs. 51.3 ppb, $p > 0.05$). The blood eosinophil count before rush-IT induction showed no association with the effectiveness of rush-HDM-IT for asthma at 2 years after rush-IT (step-down-achieved group vs. step-down-not-achieved group: 279.9/μL vs. 294.2/μL, $p > 0.05$). Finally, the HDM-specific IgE/total IgE in serum before rush-IT induction showed no association with the effectiveness of rush-HDM-IT for asthma at 2 years after the induction of rush-IT (step-down-achieved group vs. step-down-not-achieved group: 7.8% vs. 4.1%, $p > 0.05$). Therefore, we could not detect any predictive biomarkers for the effectiveness of rush-HDM-IT and the subsequent maintenance SCIT for asthma in this study.

We also observed that the serum HDM-specific IgG4 concentration increased after the induction of rush-HDM-IT; however, it showed no association with the effectiveness of rush-HDM-IT for asthma at 2 years after rush-IT (data not shown). The serum HDM-specific IgE concentration did not differ between the rush-HDM-IT group and the control group (data not shown).

Changes in HDM-induced IL-5 and IL-13 production from PBMCs

Lastly, we examined the changes in HDM-induced IL-5 and IL-13 production from PBMCs to assess the changes in specific allergen-induced Th2-mediated systemic immune responses.

https://doi.org/10.5415/apallergy.2021.11.e32

Asia Pacific allergy

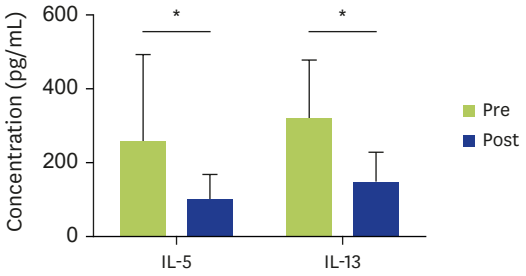

Fig. 3. *Dermatophagoides farinae*-induced interleukin (IL)-5 and IL-13 production from peripheral blood mononuclear cells before and after rush-HDM-IT. The levels of IL-5 and IL-13 were measured in the supernatants. *$p < 0.05$ when compared with cytokine production before rush-HDM-IT (pre). HDM-IT, house dust mite-immunotherapy.

We analyzed the IL-5 and IL-13 production from PBMCs before rush-HDM-IT and during the maintenance phase (1 year after rush-HDM-IT) in 7 patients of the rush-HDM-IT group versus 7 patients of the control group. The *Df*-induced IL-5 production from PBMCs was suppressed by rush-HDM-IT (**Fig. 3**). Furthermore, the *Df*-induced IL-13 production from PBMCs was also suppressed by rush-HDM-IT (**Fig. 3**). In the control group, the *Df*-induced IL-5 production from PBMCs increased, whereas the *Df*-induced IL-13 production remained unchanged (data not shown). Similar results were observed in PBMCs obtained 2 years after rush-HDM-IT (data not shown). These findings suggested that rush-HDM-IT and maintenance SCIT suppressed allergen-induced Th2-mediated systemic immune responses.

DISCUSSION

In this study, we introduced and conducted rush-IT using the standardized purified HDM allergen in HDM-sensitized Japanese asthmatics, and found that rush-HDM-IT is relatively safe and, importantly, effective for asthma. Although 4 patients (30.7%) had a SR and 3 patients (23.1%) had anaphylaxis, they were not severe and all patients recovered within a short time. Rush-HDM-IT and the subsequent maintenance SCIT improved the treatment step of asthma and reduced the dose of ICS. Furthermore, rush-HDM-IT suppressed the HDM-induced IL-5 and IL-13 production from PBMCs, suggesting that the clinical effectiveness of this treatment is associated with suppressed allergen-induced Th2-mediated systemic immune responses.

Rush-HDM-IT could be relatively safely performed in Japanese asthmatics in this study. The incidence of SR events in conventional SCIT has been reported to be 0.84%–28.6% per patient and 0.6% per injection [5-7]. Rush-SCIT has a higher incidence of SR than conventional SCIT [5-12]. The incidence of SR events in rush-SCIT has been reported to be 27%–100% per patient treated with rush-IT without premedication, 7.2%–27% per patient treated with rush-IT plus premedication [5-7], and 1.3% per injection [8]. In this study, we conducted AIT using rush-IT, and the incidence of SR events was therefore expected to be higher than that of conventional SCIT. The incidence of SR events in this study was 30.8% (**Table 2**), which is in line with the other reports. None of the cases of anaphylaxis were severe (grade 3 in the WAO systemic allergic reaction grading system), and all patients recovered within a short time. In addition, all cases of anaphylaxis occurred when >100 JAU (0.1 mL of 1,000 JAU/mL) of HDM allergen was injected. Considering the possibility that diluted allergen solutions (<1,000 JAU/mL) are easily deactivated, since this study was performed, we

https://doi.org/10.5415/apallergy.2021.11.e32

have changed the management of diluted HDM solutions of <1,000 JAU/mL from 2 months of storage to a ready-to-use preparation. Ever since we made this change, no patients have experienced anaphylaxis during rush-HDM-IT (data not shown), although the number of observed patients has been small. Therefore, in this study, it is possible that the diluted allergen solutions <1,000 JAU/mL were deactivated and did not work, and when the patients were injected with 1,000 JAU/mL of HDM, it may have actually been a sudden and large increase in allergen, which may have contributed to the higher incidence of SR events in this study. We would like to examine the effects of the management of diluted HDM solutions on the incidence of SR events in the future.

Several reports have suggested that HDM-SCIT is effective for bronchial asthma [22-25]. Furthermore, meta-analyses have confirmed the effect of SCIT on asthma such as the improvement of asthma symptoms and airway hyperreactivity, and the reduction of drug requirements [26, 27]. In this study, we found that rush-HDM-IT induction and the subsequent maintenance SCIT improved the treatment step of asthma and reduced the amount of ICS used even after guideline-based asthma treatment has been performed (**Fig. 1**). The effect of the addition of HDM-SCIT to the guideline-based asthma treatment in HDM-sensitized asthma has already been reported [28]. Adding HDM-SCIT decreased the frequency of inhaled β2-agonist usage and improved in peak flow [28]. In pediatric asthma, adding HDM-SCIT to the guideline-based asthma treatment reduced the ICS requirement and increased the morning peak flow [29]. Moreover, Baris et al. [30] reported that adding HDM-SCIT to pharmacotherapy in childhood asthma suppressed the total asthma symptom score, total symptom score, and total medication scores at the end of 1 year as compared to pharmacotherapy alone. These findings suggested that HDM-SCIT provides additional benefits in asthma even after the standard treatment has already been performed, which is consistent with our results.

We could not confirm the effect of rush-HDM induction and maintenance SCIT on the symptoms of asthma or rhinitis in this study (**Fig. 2**). We consider that the lack of an effect was probably due to the fact that we introduced rush-IT when the asthma or rhinitis was already well-controlled. Therefore, the symptom scores and disease control at baseline were already in a good condition, and it was thus difficult to demonstrate any effect on the symptom scores and disease control.

The asthma phenotypes for which AIT is effective remain to be established. Hoshino et al. [31] reported that HDM-SLIT is effective in asthma with high FeNO or high serum periostin levels, suggesting that the effect of AIT may be higher in type 2-dominant asthma. Di Lorenzo et al. [32] reported that the therapeutic effect of AIT is high in patients with a specific IgE/total IgE of 16.2 or higher. Consequently, in this study, we measured the FeNO, blood eosinophil count, and HDM IgE/total IgE before the induction of rush-IT, then compared these biomarkers between the step-down-achieved group and the step-down-not-achieved group. However, we could not find any predictive biomarker for the response to rush-HDM-IT and maintenance SCIT in asthma patients in this study; this may have been due to the small sample size.

Rush-HDM-IT suppressed the HDM-induced IL-5 and IL-13 production from PBMCs (**Fig. 3**). As most PBMCs are lymphocytes, our results suggested that rush-HDM-IT suppressed allergen-induced Th2 cytokine production from lymphocytes. These results suggested that the clinical benefits observed in our study were attributable to, at least in part, the reduced production of type 2 cytokines, including IL-5 and IL-13.

https://doi.org/10.5415/apallergy.2021.11.e32

There are some limitations. This study was conducted in a single institution and the number of cases is too small. Another limitation is that there was no defined rule for step-down of the treatment or reduction of the drug including ICS. Although step-down of asthma treatment was determined by the physician attended in this study, distribution of the physician is not different between the 2 groups.

In conclusion, rush-HDM-IT and the subsequent maintenance SCIT are tolerable and clinically effective in HDM-sensitive Japanese asthmatics even after standard treatment has already been performed. AIT is the only existing treatment that can be expected to induce immunological remission, that is, it may cure some cases with allergic diseases. Therefore, it is hoped that AIT will become more widely applied for the treatment of asthma as a strategy to modify the disease course.

ACKNOWLEDGEMENTS

This study was funded by a grant from the Ministry of Education, Culture, Sports, Science and Technology (15K09228). We would like to thank Dr Katsuyo Ohashi-Doi and Hiroki Matsuhara (Torii Pharmaceutical Co., Ltd.) for giving us *Df* extract. We would like to thank Ms. Akemi Yokote for her excellent technical assistance.

SUPPLEMENTARY MATERIAL

Supplementary material 1 can be found via 10.5415/apallergy.2021.11.e32

Supplementary material 1
Example of a schedule for rush-HDM-IT

Click here to view

REFERENCES

1. Nagata M, Nakagome K. Allergen immunotherapy in asthma: current status and future perspectives. Allergol Int 2010;59:15-9.
PUBMED | CROSSREF
2. Nakagome K, Nagata M. Role of allergen immunotherapy in asthma treatment and asthma development. Allergies 2021;1:33-45.
CROSSREF
3. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, Suzaki H, Fujieda S, Masuyama K; Japanese Society of Allergology. Japanese guidelines for allergic rhinitis 2020. Allergol Int 2020;69:331-45.
PUBMED | CROSSREF
4. Jacquet A. The role of innate immunity activation in house dust mite allergy. Trends Mol Med 2011;17:604-11.
PUBMED | CROSSREF
5. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol 2006;97:126-37.
PUBMED | CROSSREF
6. Cox L. Allergen immunotherapy: immunomodulatory treatment for allergic diseases. Expert Rev Clin Immunol 2006;2:533-46.
PUBMED | CROSSREF

7. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125:569-74.
PUBMED | CROSSREF

8. Temiño VM, Wu P, Konig J, Fahrenholz JM. Safety of multiple aeroallergen rush immunotherapy using a modified schedule. Allergy Asthma Proc 2013;34:255-60.
PUBMED | CROSSREF

9. Kim ME, Kim JE, Sung JM, Lee JW, Choi GS, Nahm DH. Safety of accelerated schedules of subcutaneous allergen immunotherapy with house dust mite extract in patients with atopic dermatitis. J Korean Med Sci 2011;26:1159-64.
PUBMED | CROSSREF

10. Winslow AW, Turbyville JC, Sublett JW, Sublett JL, Pollard SJ. Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy. Ann Allergy Asthma Immunol 2016;117:542-5.
PUBMED | CROSSREF

11. Smits WL, Giese JK, Letz KL, Inglefield JT, Schlie AR. Safety of rush immunotherapy using a modified schedule: a cumulative experience of 893 patients receiving multiple aeroallergens. Allergy Asthma Proc 2007;28:305-12.
PUBMED | CROSSREF

12. Casanovas M, Martín R, Jiménez C, Caballero R, Fernández-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. Int Arch Allergy Immunol 2006;139:153-8.
PUBMED | CROSSREF

13. Nakamura Y, Tamaoki J, Nagase H, Yamaguchi M, Horiguchi T, Hozawa S, Ichinose M, Iwanaga T, Kondo R, Nagata M, Yokoyama A, Tohda Y; Japanese Society of Allergology. Japanese guidelines for adult asthma 2020. Allergol Int 2020;69:519-48.
PUBMED | CROSSREF

14. Global Initiative for Asthma. Global strategy for the diagnosis and prevention. (updated 2020) [Internet]. Fontana (WI): The Global Initiative for Asthma; 2020 [cited 2020 Dec 31]. Available from: https://ginasthma.org/reports/

15. Nagata M, Yamamoto H, Tabe K, Kimura I, Houya I, Kuramitsu K, Kiuchi H, Yanagihara Y, Sakamoto Y, Yamamoto K, Dohi Y. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: changes in in vivo and in vitro responses to HDM. Intern Med 1993;32:702-9.
PUBMED | CROSSREF

16. Nagata M, Saito K, Kikuchi I, Tabe K, Hagiwara K, Kanazawa M, Sakamoto Y. Immunotherapy attenuates eosinophil transendothelial migration induced by the supernatants of antigen-stimulated mononuclear cells from atopic asthmatics. Int Arch Allergy Immunol 2004;134 Suppl 1:21-4.
PUBMED | CROSSREF

17. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472.
PUBMED | CROSSREF

18. Ohta K, Jean Bousquet P, Akiyama K, Adachi M, Ichinose M, Ebisawa M, Tamura G, Nagai A, Nishima S, Fukuda T, Morikawa A, Okamoto Y, Kohno Y, Saito H, Takenaka H, Grouse L, Bousquet J. Visual analog scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. J Asthma 2013;50:514-21.
PUBMED | CROSSREF

19. Nagata M, Shibasaki M, Sakamoto Y, Fukuda T, Makino S, Yamamoto K, Dohi Y. Specific immunotherapy reduces the antigen-dependent production of eosinophil chemotactic activity from mononuclear cells in patients with atopic asthma. J Allergy Clin Immunol 1994;94:160-6.
PUBMED | CROSSREF

20. Nagata M, Tabe K, Hong Choo J, Sakamoto Y, Matsuo H. Effect of immunotherapy on the production of eosinophil adhesion-inducing activity from mononuclear cells in house-dust-mite-sensitive bronchial asthma. Int Arch Allergy Immunol 1998;117 Suppl 1:20-3.
PUBMED | CROSSREF

21. Ueda Y, Nakagome K, Kobayashi T, Noguchi T, Soma T, Ohashi-Doi K, Tokuyama K, Nagata M. Dermatophagoides farinae upregulates the effector functions of eosinophils through αMβ2-integrin and protease-activated receptor-2. Int Arch Allergy Immunol 2019;178:295-306.
PUBMED | CROSSREF

22. Pichler CE, Marquardsen A, Sparholt S, Løwenstein H, Bircher A, Bischof M, Pichler WJ. Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. Allergy 1997;52:274-83.
PUBMED | CROSSREF

23. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. Clin Exp Allergy 2003;33:1076-82.
PUBMED | CROSSREF

24. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM; Regione Veneto Study Group on the "Effect of immunotherapy in allergic asthma". Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 2004;113:643-9.
PUBMED | CROSSREF

25. Basomba A, Tabar AI, de Rojas DH, García BE, Alamar R, Olaguíbel JM, del Prado JM, Martín S, Rico P. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. J Allergy Clin Immunol 2002;109:943-8.
PUBMED | CROSSREF

26. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74.
PUBMED | CROSSREF

27. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, Muraro A, Roberts G, Akdis CA, Bonini M, Cavkaytar O, Flood B, Gajdanowicz P, Izuhara K, Kalayci Ö, Mosges R, Palomares O, Pfaar O, Smolinska S, Sokolowska M, Asaria M, Netuveli G, Zaman H, Akhlaq A, Sheikh A. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy 2017;72:1825-48.
PUBMED | CROSSREF

28. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 2004;113:643-9.
PUBMED | CROSSREF

29. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. J Allergy Clin Immunol 2010;126:942-9.
PUBMED | CROSSREF

30. Baris S, Kiykim A, Ozen A, Tulunay A, Karakoc-Aydiner E, Barlan IB. Vitamin D as an adjunct to subcutaneous allergen immunotherapy in asthmatic children sensitized to house dust mite. Allergy 2014;69:246-53.
PUBMED | CROSSREF

31. Hoshino M, Akitsu K, Kubota K, Ohtawa J. Association between biomarkers and house dust mite sublingual immunotherapy in allergic asthma. Clin Exp Allergy 2020;50:1035-43.
PUBMED

32. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, Ditta V, Lo Bianco C, Leto-Barone MS, D'Alcamo A, Di Fede G, Rini GB, Ditto AM. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol 2009;123:1103-10.
PUBMED | CROSSREF