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Letter to the Editor

Dual sublingual immunotherapy with Japanese Cedar Pollen droplets and House Dust Mite tablets

Dear Editor,

Japanese cedar pollinosis (JCP-PS) is a common disorder in Japan,^{1,2} and the majority of patients are also sensitized to other allergens, especially HDM.³ Until recently, allergen-specific immunotherapy of patients with JCP-PS and HDM allergic rhinitis (HDM-AR) was performed by subcutaneous administration of the two allergens. However, two drugs for sublingual immunotherapy (SLIT) were recently introduced; namely, Japanese Cedar Pollen droplets⁴ (JCP-D; CEDARTOLEN[®]) in 2014 and House Dust Mite tablets⁵ (HDM-T; MITICURE[®]) in 2015. Although we believe that dual SLIT with these two allergens may be more convenient for Japanese patients co-sensitized to JCP and HDM, no prospective trials have been conducted to establish the safety of this dual immunotherapy. Therefore, we investigated the safety of dual-SLIT as a preliminary trial of 11 subjects with concurrent JCP-PS and HDM-AR. It was the first prospective and interventional trial and it can be defined as Phase I. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Yamanashi. Written informed consent was obtained from all subjects.

The 11 subjects comprised 4 men and 7 women of average age 35.6 years (standard deviation [SD] 13.4 years; [Supplementary Table 1](#)). The mean ($\pm$ SD) IgE levels specific for JCP and HDM (*Der p* and *Der f*) allergens were 3.36 ± 0.48 kU/L, 3.73 ± 1.66 kU/L, and 3.55 ± 1.44 kU/L, respectively. Complications were as follows: bronchial asthma ($n = 2$), atopic dermatitis ($n = 2$), urticaria ($n = 2$), and drug allergy ($n = 1$). Subjects were not allowed to receive any immunosuppressant or anticancer drugs during the trial. Safety was evaluated based on the incidence, severity, timing of onset, and duration of adverse events (AEs) and AEs related with JCP-D or/and HDM-T (adverse drug reactions: ADRs) according to the Common Terminology Criteria for Adverse Events version 4.0.⁶ SLIT-specific local reactions were evaluated according to the World Allergy Organization grading system.⁷ A total of 10 subjects received JCP-D followed by add-on HDM-T between October 2016 and May 2017 ([Supplementary Fig. 1](#)).

In the dosing regimen, the patients received JCP-D alone for 4–5 weeks, and HDM-T was then administered concurrently for an additional 24 weeks. JCP-D was administered at 40–2000 Japanese allergy units (JAU)/day for 2 weeks and then at 2000 JAU/day thereafter. HDM-T was administered at 3300 JAU/day for 1 week

followed by 10,000 JAU/day thereafter. When both allergens were administered on the same day, JCP-D was placed and held under the tongue for 2 min, the patient rested for 5 min, and HDM-T was then placed and held under the tongue for 1 min. Each holding time is based on each usage approved by Japanese regulatory authority.

During the initial 4–5 weeks of SLIT with JCP-D alone, AEs occurred in 10 of 11 subjects (90.9%). One patient withdrew from the trial on the first day of JCP-D administration due to urticaria. During dual-SLIT with JCP-D and HDM-T, AEs occurred in 8 of the 10 subjects (80.0%). A total of 32 AEs were recorded over the 28-week trial period, and all were considered to be of mild-to-moderate severity ([Table 1](#)). The ADRs observed are indicated in [Figure 1](#). During JCP-D, a total of 13 ADRs occurred, 4 of which persisted into the dual-SLIT period but did not increase in severity during that time. Seventeen new ADRs occurred after HDM-T was introduced. The most common ADRs were runny nose (4 events; 2 each with JCP-D and dual-SLIT), pharynx strange sensation (4 events; 1 with JCP-D, 3 with dual-SLIT), and ear itching (3 events, all during dual-SLIT) which were all SLIT-specific local reactions. All ADRs were mild-to-moderate in severity. The moderate ADRs were eye itching (1 event with JCP-D [treated with medication]), urticaria (1 event with JCP-D [discontinued subject]), and ear itching (1 event with dual-SLIT). Of the 13 ADRs that occurred during JCP-D treatment, 12 (92.3%) occurred on the first day of dosing, and 7 (53.8%) and 8 (61.5%) of the ADRs resolved within 2 and 4 weeks, respectively. Of the 17 ADRs that occurred after initiation of dual-SLIT, 9 (52.9%) occurred on the first day of dosing with HDM-T, and 12 (70.6%) and 16 (94.1%) of the ADRs resolved within 2 and 4 weeks, respectively ([Supplementary Table 2](#)). The nature of the ADRs and the timing of their onset and resolution in this trial were similar to those commonly observed in clinical trials of the individual SLIT drugs.

Globally, only a few clinical studies have been performed of dual-SLIT therapy for allergy.^{9,10} Maloney *et al.*⁹ proposed that dual-SLIT therapy should be performed with the first drug administered in the morning and the second in the evening. In Japan, the prescribing instructions restrict exercise for 2 h before and after administration of SLIT drugs, which may interfere with patients' daily lives. Therefore, we designed the present trial to administer JCP-D and HDM-T 5 min apart. Since most ADRs with a single SLIT drug occur within 4 weeks of first administration, and ADRs

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Table 1

List of adverse events.

JCP-D alone (4 or 5 weeks)			JCP-D and HDM-T (24 weeks)		
(n = 11)			(n = 10)		
Patients (%)	9 (81.8)		Patients (%)	8 (80.0)	
Total AEs	14		Total AEs	18	
Discontinuation (n)	1 [†]		Discontinuation (n)	0	
Symptom	Grade	No. of AEs	Symptom	Grade	No. of AEs
Runny nose [‡]	1	2	Pharynx strange sensation[§]	1	3
Pharynx strange sensation^{‡,§}	1	1	Runny nose	1	2
Eye itching [‡]	2	1	Ear itching[§]	1	2
Sneezing	1	1		2	1
Dizziness	1	1	Oral swelling[‡]	1	1
Allergic reaction (skin redness)	1	1	Swollen tongue[§]	1	1
Pruritus (skin of the neck)	1	1	Glossitis[§]	1	1
Glossitis[§]	1	1	Lip pruritus and Lip swelling[§]	1	1
Malaise	1	1	Nasal congestion	1	1
Rhinitis allergic [‡]	1	1	Cough	1	1
Cough	1	1	Dyspnoeas	1	1
Hoarseness [¶]	1	1	Nausea	1	1
Urticarias [‡]	2	1	Allergic reaction (skin redness)	1	1
			Pruritus (skin of the flank) [¶]	1	1

JCP, Japanese cedar pollen; HDM, House dust mite; AE, adverse event.

Adverse events specific to SLIT are indicated in bold.

[†] Treatment discontinued on the subject's request.[‡] Each one of adverse events, where symptoms persisted even after starting co-administration of JCP-D and HDM-T, was also included in the sum total of adverse events occurring after initiation of co-administration.[§] Adverse event specific to sublingual immunotherapy (Grading System for SLIT Local AEs; WHO position paper, 2013).[¶] A causal relationship with the test drugs can be ruled out.

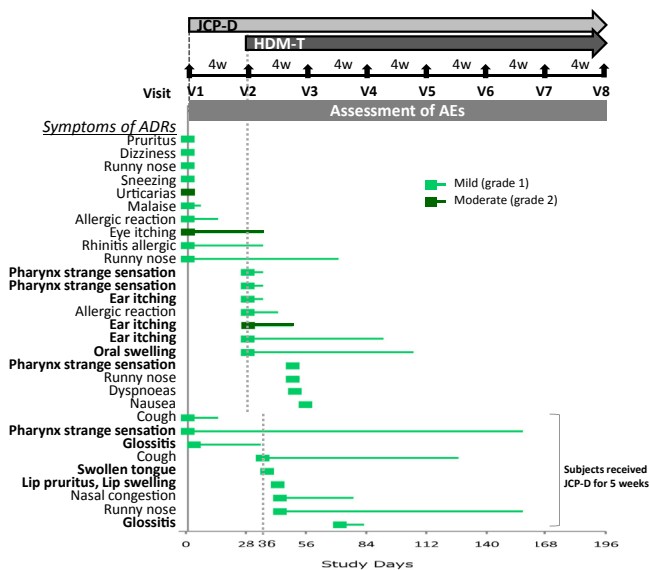


Fig. 1. Symptoms, severity, day of onset, and duration of adverse drug reactions. The duration of an ADR is defined as the number of treatment days from onset to resolution. Adverse events specific to SLIT are indicated in bold font. ADR, adverse drug reaction; AE, adverse event; HDM-T, HDM tablet; JCP-D, JCP droplet; V, visit; w, week.

in the oral cavity may be intensified by exposure to multiple allergens, we designed our dosing regimen such that JCP-D was administered alone for 4 weeks before introduction of HDM-T.

In conclusion, we propose a new dual-SLIT regimen using two different allergens, such as JCP-D and HDM-T, which is appropriate for patients in Japan. In this regimen, the first SLIT drug is administered and patients are observed for ≥ 4 weeks before initiation of the second drug. Our data suggest that this regimen contributes to conducting dual-SLIT with JCP-D and HDM-T more safely. Further safety and efficacy studies should be performed to validate our findings, including larger trials and trials that test dual-SLIT with HDM-T administration first. Especially, a trial to investigate the safety of the regimen for dual-SLIT with HDM-T administration first should be conducted in order to dual-SLIT becomes a common therapy in the clinical practice.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.03.005>.

Conflict of interest

TM received a lecture fee and research funding from Torii Pharmaceutical. CF, KDO and KN are employed by Torii Pharmaceutical. KM received a lecture fee from Torii Pharmaceutical. The rest of the authors have no conflict of interest.

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Supplementary Table 1 Subject characteristics

Age (y), mean $\pm$ SD		35.6 $\pm$ 13.4 (14–57)	
Male : female		4:7 (n = 11)	
Specific IgE (kU/L)	Japanese cedar	3.36 $\pm$ 0.48	Class 3–4
	Japanese cypress	2.27 $\pm$ 0.44	Class 2–3
	House dust mite 1: <i>Dermatophagoides pteronyssinus</i>	3.73 $\pm$ 1.66	Class 2–6
	House dust mites 2: <i>Dermatophagoides farinae</i>	3.55 $\pm$ 1.44	Class 2–6
Complications (no. of subjects)		Bronchial asthma: 2 Atopic dermatitis: 2 Urticaria: 2 Drug allergy: 1	

Supplementary Table 2 Time of onset and time to disappearance of side effects

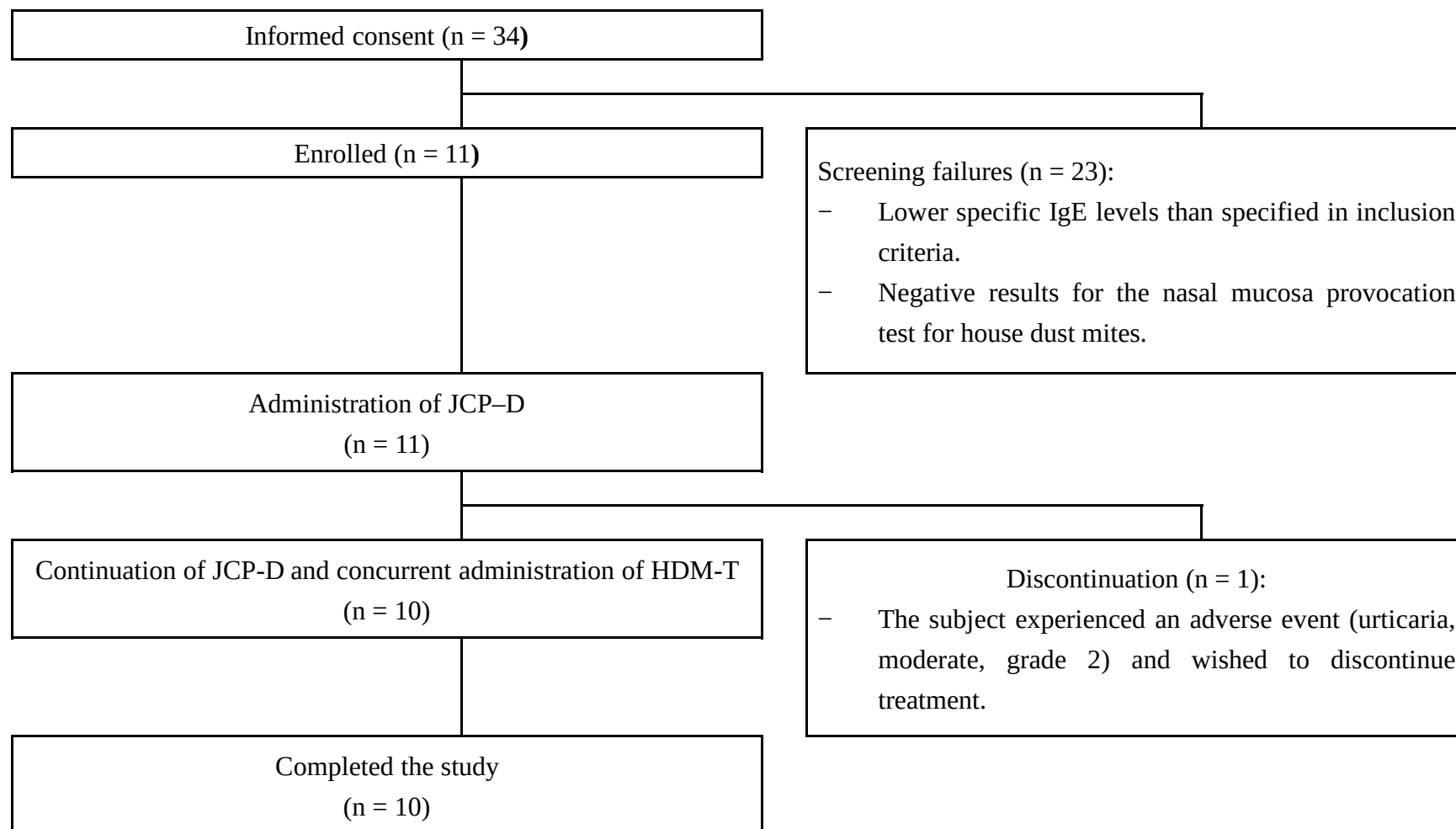
JCP-D alone (n = 11)			JCP-D and HDM-T (n = 10)	
Onset of ADRs	Weeks after start of SLIT	No. of AEs	Weeks after start of dual SLIT	No. of AEs
	1	13	1	11
	2	0	2	1
	3	0	3	0
	4	0	4	4
	Total	13	5	0
			6	1
			Total	17
Disappearance of ADRs	Duration from onset	No. of AEs	Duration from onset	No. of AEs
	The day of onset	1	The day of onset	4
	< 1w	5	< 1w	2
	< 2w	1	< 2w	4
	< 1mo	1	< 1mo	2
	> 1mo	5	> 1mo	5
	Total	13	Total	17

JCP, Japanese cedar pollen; HDM, House dust mite; ADRs, adverse drug reaction; w, week; mo, month.

Supplementary Table 3 Major allergen content of JCP-D and HDM-T

Major allergen	Major allergen content ($\mu\text{g/mL}$)		
	JCP-D alone (2,000JAU/mL)	HDM-T alone (10,000JAU/mL PBS)	Mixture of JCP-D and HDM-T ¹⁾
Cry j 1	3.16 ± 0.10	-	3.13 ± 0.11
Der f 1	-	1.84 ± 0.10	1.84 ± 0.06
Der p 1	-	1.76 ± 0.10	1.61 ± 0.03

JAU; Japanese Allergy Unit defined by the Japanese Society of Allergology; JCP, Japanese cedar pollen; HDM, House dust mite



Supplementary Fig. 1. Subject Disposition
HDM-T, HDM tablet; JCP-D, JCP droplet.