




# Efficacy of dual sublingual immunotherapy with Japanese cedar pollen and house dust mite allergens in patients with allergic rhinitis sensitized to multiple allergens

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## Abstract

**Objective:** In the present study, we examined the effects of dual sublingual immunotherapy (SLIT) with Japanese cedar pollen (JCP) and house dust mite (HDM) allergens on nasal symptoms during the peak pollen period (PPP) and in late fall (LF) in patients with allergic rhinitis (AR) sensitized to both JCP and HDM. We then compared the efficacy of dual-SLIT with JCP and HDM to that of mono-SLIT with JCP at PPP.

**Methods:** Twenty-five bisensitized patients with AR who showed positive serum specific immunoglobulin E (IgE) against both JCP and HDM were enrolled. In dual-SLIT, 16 patients received JCP drops/tablets and HDM tablets concurrently. In mono-SLIT with JCP, nine patients received JCP drops/tablets. Nasal symptoms were scored on a 0–4 point scale.

**Results:** The nasal scores at PPP and in LF in the bisensitized patients with AR who received dual-SLIT with JCP and HDM in 2019 were significantly lower than those in the same patients who received antihistamines only in 2018. The decrease in scores of nasal obstruction at PPP from 2018 to 2019 in patients who received dual-SLIT was significantly greater than those in patients who received mono-SLIT with JCP. Dual-SLIT was well tolerated and only had mild adverse effects.

**Conclusion:** These findings suggest that dual-SLIT suppressed both JCP-induced seasonal and HDM-induced perennial nasal symptoms in bisensitized patients with AR. Dual-SLIT was more effective in suppressing nasal obstruction at PPP than mono-SLIT with JCP with limitation of baseline characteristics not to be controlled between the two groups, suggesting that dual-SLIT suppressed

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HDM-induced priming effects, thus resulting in further suppression of nasal obstruction at PPP.

**Level of Evidence:** 3b, a case-controlled study

**KEYWORDS**

allergic rhinitis, dual sublingual immunotherapy, house dust mite, Japanese cedar pollen

## 1 | INTRODUCTION

Japanese cedar pollinosis is the most common form of allergic rhinitis (AR) in Japan, and was estimated to affect approximately 27% of the Japanese population in a 2008 epidemiological study, which reported an increase in prevalence of approximately 10% compared to an earlier study conducted in 1998.<sup>1</sup> It has been recently reported that majority of patients with Japanese cedar pollinosis is also sensitized to other allergens, especially house dust mites (HDM).<sup>2,3</sup> In polysensitized patients with AR, nasal symptoms become serious, perennial, and intractable.<sup>4</sup>

Allergen-specific immunotherapy can offer a cure in patients with AR by modulating immune responses.<sup>5</sup> Recently, drops and tablets containing Japanese cedar pollen (JCP) allergens were introduced for sublingual immunotherapy (SLIT) in Japan. More recently, tablets containing HDM allergens have also been introduced. The efficacy and safety of mono-SLIT with JCP or HDM allergens have been reported in patients with Japanese cedar pollinosis or HDM-induced AR, respectively.<sup>6–12</sup> As most patients with Japanese cedar pollinosis are sensitized to HDM, dual-SLIT with simultaneous administration of JCP and HDM allergens is expected to be more effective. Although the safety of dual-SLIT with grass and ragweed allergens<sup>13</sup> as well as with JCP and HDM allergens<sup>14,15</sup> have been reported, there is insufficient evidence regarding the efficacy of dual-SLIT in patients sensitized to multiple antigens.

In the present study, we enrolled AR patients sensitized to both JCP and HDM. We examined the effects of dual-SLIT with JCP and HDM allergens on the nasal symptoms and troubles with daily life of patients during the peak cedar pollen period or in late fall (LF), when nasal symptoms become the highest during the peak period of JCP dispersal in patients with Japanese cedar pollinosis and exacerbations mostly occur in LF in patients with HDM-induced AR in Japan.<sup>16</sup> We then compared the efficacy of dual-SLIT with JCP and HDM allergens to that of mono-SLIT with JCP allergens at the peak cedar pollen period in bisensitized patients with AR.

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

The present study was conducted at JA Kochi Hospital, which is a branch hospital of Tokushima University Hospital. A total of 25 patients (14 men, 11 women; mean age: 25.4 years) who

complained of nasal symptoms from both Japanese cedar pollinosis and HDM-induced AR participated in this study (Table 1). All patients tested positive for the CAP-radioallergosorbent test (>class 2) with serum allergen-specific IgE against both JCP and HDM. They also manifested obvious nasal symptoms of Japanese cedar pollinosis during at least the previous two cedar pollen seasons, as well as perennial nasal symptoms even outside the cedar pollen season. Among them, 16 patients (10 men, 6 women; mean age: 15.8 years) received dual-SLIT with JCP drops ( $n = 3$ ) or tablets ( $n = 13$ ) as well as HDM tablets, while nine patients (four men, five women; mean age: 42.4 years) received mono-SLIT with JCP drops ( $n = 7$ ) or tablets ( $n = 2$ ). This retrospective study was approved by the Committee for Medical Ethics of Tokushima University Hospital (#3789).

### 2.2 | Sublingual immunotherapy

JCP tablets or drops and SQ HDM tablets (Torii Pharmaceutical Co. Ltd.) were used for SLIT. JCP drops were administered daily at an initial dose of 40–2000 Japanese allergy units (JAU)/day for 2 weeks and then at a maintenance dose of 2000 JAU/day thereafter. As to JCP tablets, 2000 JAU tablets and 5000 JAU tablets are available, and 2000 JAU tablets containing JCP at an initial dose of 2000 JAU were daily administered for 1 week and then 5000 JAU tablets containing JCP at a maintenance dose of 5000 JAU were daily administered thereafter. SQ HDM tablets were administered daily at 3300 JAU/day for 1 week and then at a maintenance dose of 10,000 JAU/day

**TABLE 1** Background of patients

	Dual SLIT	JCP SLIT
Sex (male:female)	10:6	4:5
Age (year)	15.3 ± 14.0	42.4 ± 19.9
Severity of JC pollinosis		
Most severe	12	4
Severe	4	4
Moderate	0	0
Mild	0	1
Type of disease		
Sneezing and rhinorrhea type	5	4
Nasal blockage type	7	1
Combined type	4	4

Abbreviations: JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy.

thereafter. Patients were instructed to place tablets or drops under their tongues and to keep them for 1 or 2 min before swallowing. They were also requested to place nothing else in their mouth and to refrain from gargling for 5 min after swallowing. In dual-SLIT with JCP and HDM, 16 patients first received JCP drops ( $n = 3$ )/tablets ( $n = 13$ ) or HDM tablets alone for at least more than 4 weeks, and then received both JCP drops/tablets and HDM tablets concurrently. In mono-SLIT with JCP, nine patients received JCP drops ( $n = 7$ )/tablets ( $n = 2$ ). Patients were allowed to use the following drugs as needed at the peak

cedar pollen period: oral medication of antihistamines and leukotriene antagonists, and intranasal spray of corticosteroids.

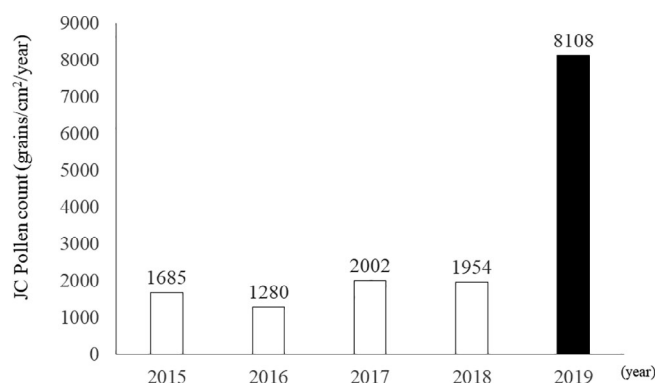
### 2.3 | Measurement of the JCP count

The number of airborne cedar pollen was measured daily using the Durham method at JA Kochi Hospital in Kochi Prefecture during the cedar pollen season. A Vaseline-coated glass slide was set on a Durham gravity sampler over 24 h and was stained with Carbela's solution.<sup>17</sup> The number of dyed pollen grains with a finger-like projection but not dye particles was counted by an optical microscope as the number of pollen grains per  $\text{cm}^2$  on the slide.

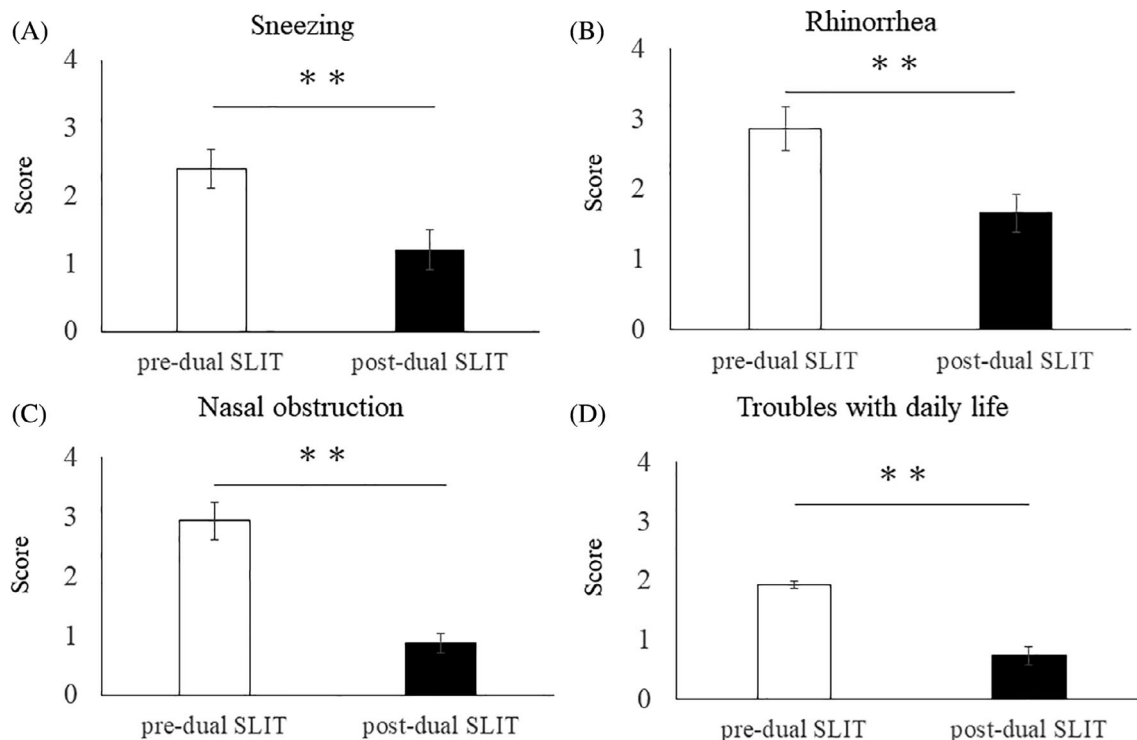
### 2.4 | Evaluation of symptoms and adverse events

Nasal symptoms were evaluated according to the Practical Guideline for the Management of Allergic Rhinitis in Japan.<sup>1</sup> Sneezing, watery rhinorrhea, nasal obstruction, and troubles with daily life were separately scored on a 0–4 point scale (0: no symptom, 1: mild, 2: moderate, 3: severe, 4: most severe).

The patients daily reported their nasal symptom scores during the peak cedar pollen period from February to March and LF from November 1 to 31 in 2018 and 2019. We compared the highest nasal symptom



**FIGURE 1** The total amount of dispersed Japanese cedar pollen (grains/ $\text{cm}^2$ /year) measured using the Durham method during the cedar pollen season from 2015 to 2019 in Kochi Prefecture



**FIGURE 2** Scores of sneezing (A), rhinorrhea (B), nasal obstruction (C), and troubles with daily life (D) at the peak cedar pollen period in patients with allergic rhinitis sensitized to both JCP and HDM allergens without any SLIT (pre-dual SLIT) in 2018 and after dual-SLIT with JCP and HDM allergens (post-dual SLIT) in 2019. Data are presented as mean  $\pm$  SEM.  $n = 16$ .  $**p < .01$  versus pre-dual SLIT. HDM, house dust mite; JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy

score at the peak cedar pollen period and in LF between pre-dual SLIT in 2018 and post-dual SLIT in 2019 in 16 patients who received dual-SLIT with JCP and HDM allergens. We also compared the highest nasal symptom score at the peak cedar pollen period in 2019 among 16 patients who received dual-SLIT with JCP and HDM allergens with those of nine patients who received mono-SLIT with JCP allergens.

Adverse events of dual SLIT were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0).

## 2.5 | Statistical analysis

Statistical analysis was performed using the Wilcoxon signed-rank test (Statcel version 4, OMS Publishing Inc.). Statistical significance was set at  $p < .05$ .

## 3 | RESULTS

### 3.1 | JCP counts

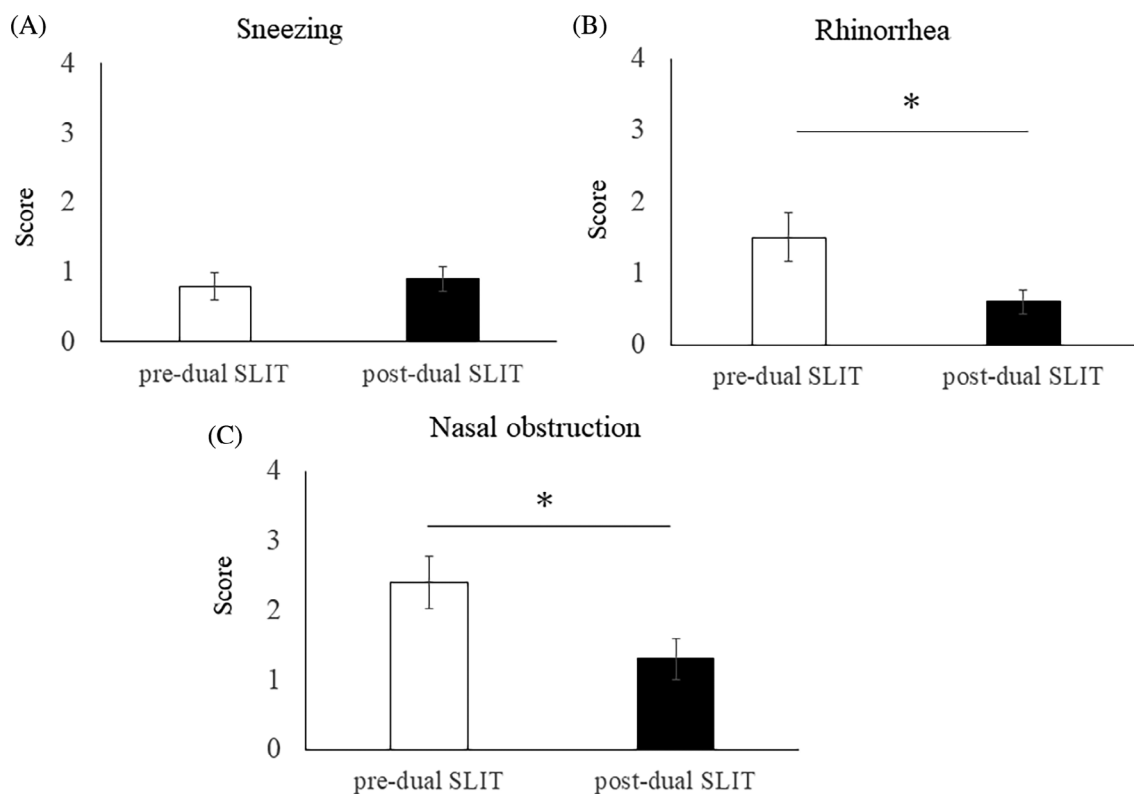
In the 2019 cedar pollen season, the total amount of dispersed JCP was 8108 grains/cm<sup>2</sup>/year, which was four times higher than that in

2018, and was the highest level detected during the last 4 years in Kochi Prefecture (Figure 1).

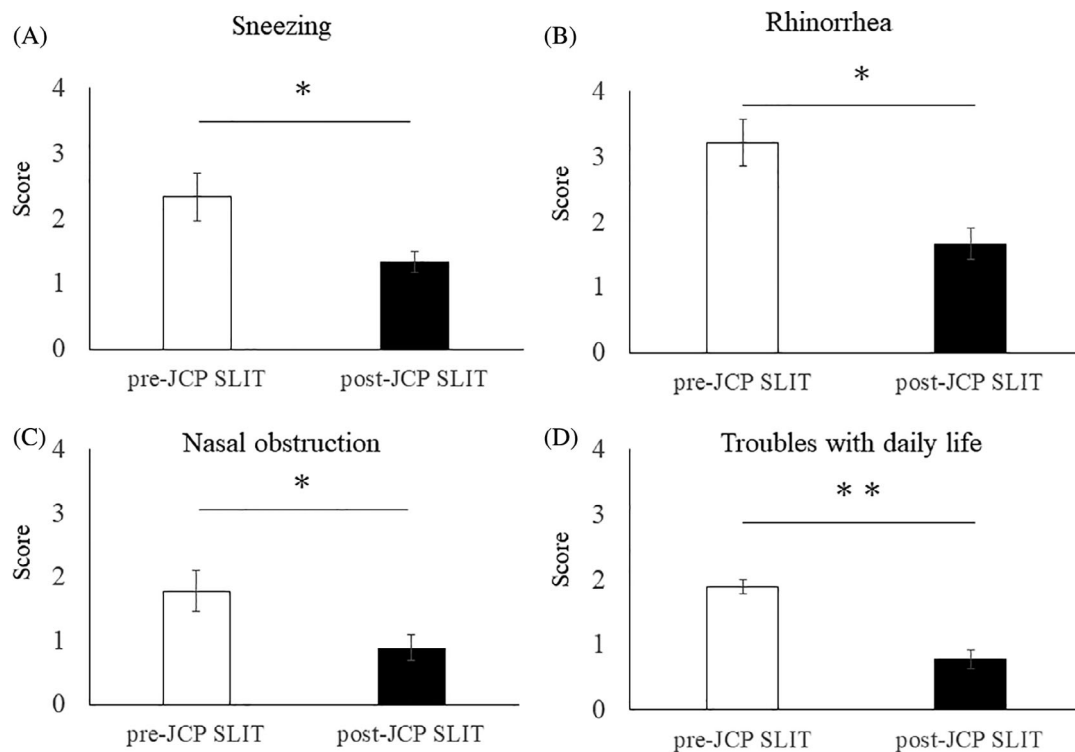
### 3.2 | Efficacy of dual SLIT with both JCP and HDM allergens

Scores of sneezing, rhinorrhea, nasal obstruction, and troubles with daily life at the peak cedar pollen period in 16 patients who received dual-SLIT with JCP and HDM allergens in 2019 were significantly lower than those in the same patients who received antihistamines before SLIT in 2018 (Figure 2). Scores of rhinorrhea and nasal obstruction but not sneezing in LF in 16 patients who received dual-SLIT with JCP and HDM allergens in 2019 were significantly lower than those in the same patients who received antihistamines before SLIT in 2018 (Figure 3).

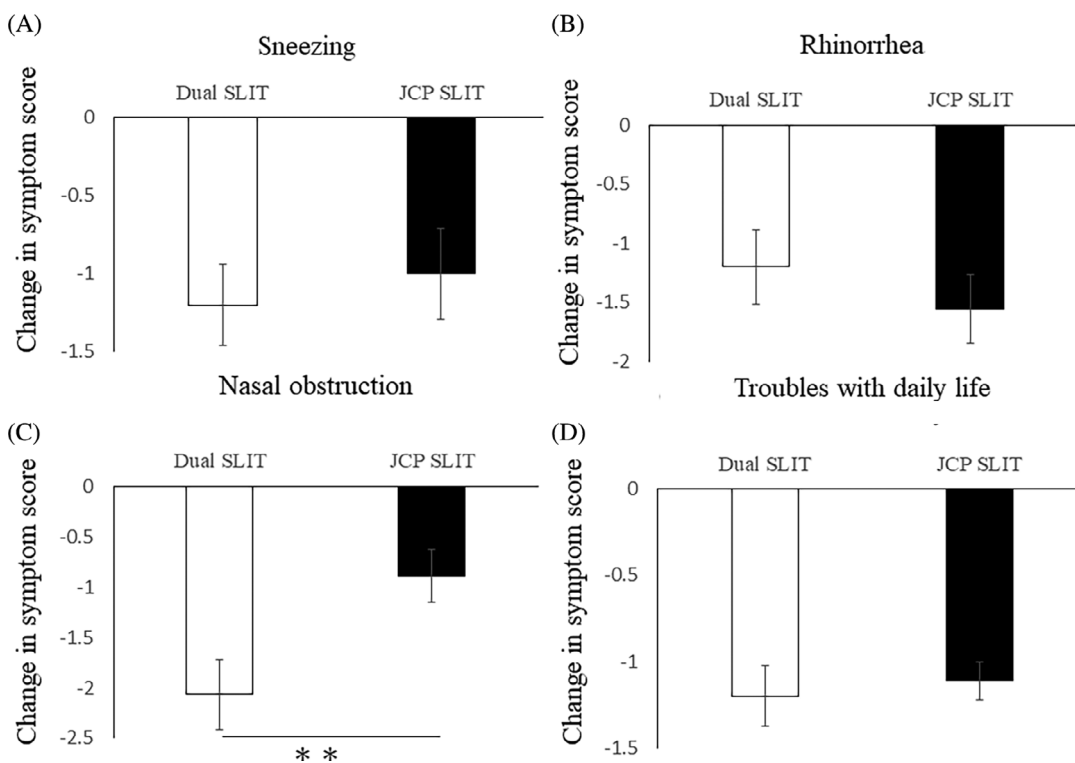
Scores of sneezing, rhinorrhea, nasal obstruction, and troubles with daily life at the peak cedar pollen period in nine patients who received mono-SLIT with JCP allergens in 2019 were significantly lower than those in the same patients received antihistamines before SLIT in 2018 (Figure 4). There was a decrease in scores of nasal obstruction, but not sneezing, rhinorrhea, and troubles with daily life during the peak cedar pollen period from 2018 to 2019 in patients receiving dual-SLIT with JCP and HDM allergens, which was



**FIGURE 3** Scores of sneezing (A), rhinorrhea (B), and nasal obstruction (C) in late fall in patients with allergic rhinitis sensitized to both JCP and HDM allergens without any SLIT (pre-dual SLIT) in 2018 and after dual-SLIT with JCP and HDM allergens (post-dual SLIT) in 2019. Data are presented as mean  $\pm$  SEM.  $n = 16$ . \* $p < .05$  versus pre-dual SLIT. HDM, house dust mite; JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy



**FIGURE 4** Scores of sneezing (A), rhinorrhea (B), nasal obstruction (C), and troubles with daily life (D) at the peak cedar pollen period in patients with allergic rhinitis sensitized to both JCP and HDM allergens without any SLIT (pre-JCP SLIT) in 2018 and after mono-SLIT with JCP allergens alone (post-JCP SLIT) in 2019. Data are presented as mean  $\pm$  SEM.  $n = 9$ . \* $p < .05$ , \*\* $p < .01$  versus pre-dual SLIT. HDM, house dust mite; JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy



**FIGURE 5** Changes in scores of sneezing (A), rhinorrhea (B), nasal obstruction (C), and troubles with daily life (D) at the peak cedar pollen period from 2018 to 2019 in patients with allergic rhinitis sensitized to both JCP and HDM allergens, who received dual-SLIT with JCP and HDM allergens (dual SLIT,  $n = 16$ ) or mono-SLIT with JCP allergens (JCP SLIT,  $n = 9$ ). Data are presented as mean  $\pm$  SEM. \*\* $p < .01$  versus JCP SLIT. HDM, house dust mite; JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy

**TABLE 2** Adverse events of SLIT

	Preceding SLIT		Dual SLIT (n = 16)	Mono SLIT (n = 9)
	JCP (n = 10)	HDM (n = 6)		
Mouth swelling	0	0	3	0
Throat irritation	0	1	2	5
Oral pruritus	0	1	0	0
Nausea	1	0	1	0
Nasal symptoms	1	0	0	1
Others	0	0	1	0

Abbreviations: HDM, house dust mite; JCP, Japanese cedar pollen; SLIT, sublingual immunotherapy.

significantly greater than that in patients receiving mono-SLIT with JCP allergens (Figure 5). There was no difference in total nasal symptom score during the peak cedar pollen period between in patients receiving dual-SLIT and in patients receiving mono-SLIT.

### 3.3 | Adverse events

In the present study, the adverse events of the preceding SLIT with JCP or HDM allergens were throat irritation, oral pruritus, nausea, and nasal symptoms. Adverse events of the subsequent dual-SLIT with addition of another antigen were mouth swelling, throat irritation, nausea, and dermatitis. There were no anaphylactic reactions, and seven patients who received dual-SLIT and six patients who received mono-SLIT showed adverse events, which were mild (grade 1 as per CTCAEv4.0) and disappeared soon without further medical evaluation and treatment (Table 2).

## 4 | DISCUSSION

In 2019, JCP dispersed in approximately four times more than it did in 2018 in Kochi Prefecture. Because the degree of nasal symptoms in patients with Japanese cedar pollinosis is associated with the dispersion of JCP,<sup>18</sup> it is expected that patients' nasal symptoms were exacerbated during the 2019 cedar pollen season. However, in the present study, dual-SLIT with JCP and HDM allergens inhibited nasal symptoms including sneezing, rhinorrhea, nasal obstruction, and troubles with daily life during the peak cedar pollen period in 2019 in AR patients sensitized to both JCP and HDM compared with pharmacotherapy before dual SLIT in 2018. These findings suggest that SLIT with JCP allergens suppressed JCP-induced nasal symptoms in bisensitized patients with AR. The efficacy of SLIT with JCP allergens in patients with Japanese cedar pollinosis has been proven in randomized controlled studies in Japan.<sup>10-12</sup>

Dual-SLIT with JCP and HDM allergens also inhibited nasal symptoms of rhinorrhea and nasal obstruction in LF in 2019 in AR patients compared with pharmacotherapy before dual SLIT in 2018. Because HDM-induced nasal symptoms are exacerbated in LF,<sup>16</sup> these findings suggest that SLIT with HDM allergens suppressed HDM-induced nasal symptoms in bisensitized patients with AR. Two types of tablets

containing HDM antigens are available in Japan. The efficacy of SLIT with both types of HDM tablets in patients with HDM-induced AR has been proven in randomized controlled studies.<sup>6,8</sup>

Moreover, during the peak pollen period in 2019, dual-SLIT with JCP and HDM allergens further inhibited nasal obstruction symptom compared to mono-SLIT with JCP allergens in bisensitized patients with AR. Marogna et al. reported that dual-SLIT with both grass and birch allergens suppressed nasal symptom scores compared to mono-SLIT with grass or birch allergens alone in seasonal AR patients sensitized to both grass and birch allergens.<sup>19</sup> Cirila et al. reported that combined subcutaneous immunotherapy (SCIT) with grass antigens and SLIT with birch/hazel antigens improved symptoms compared with mono-SCIT with grass antigens in bisensitized patients with AR, suggesting that the combined therapy reduced the priming effects due to tree allergy.<sup>20</sup> In the present study, the participants suffered from both seasonal Japanese cedar pollinosis and perennial HDM-induced AR, and dual-SLIT with JCP and HDM allergens further suppressed nasal obstruction symptom during the peak cedar pollen period compared to mono-SLIT with JCP allergens in bisensitized patients with AR. Because the priming effect results in an increase in the reactivity of the nasal mucosa after repeated exposure to allergens,<sup>21</sup> these findings suggest that the priming effect of HDM-induced persistent inflammation in the nasal mucosa exacerbates JCP-induced seasonal nasal symptoms in bisensitized patients with AR. Because it has been reported that the allergen-induced increase in nasal mucosal blood flow was greater after the pollen season compared to before,<sup>22</sup> HDM-induced priming effects on nasal hyperemia may exacerbate nasal obstruction in patients during the peak cedar pollen period. Therefore, it is suggested that dual-SLIT with JCP and HDM allergens suppressed HDM-induced priming effects, resulting in further suppressive effects on nasal symptoms during the peak cedar pollen period in bisensitized patients with AR.

Large-scale clinical trials showed mono-SLIT with grass pollen was effective in poly-sensitized patients as well as mono-sensitized patients.<sup>23</sup> However, the efficacy of dual-SLIT with multiple-allergens is inconclusive in poly-sensitized patients. The present finding that in bisensitized patients, dual-SLIT with JCP and HDM allergens suppressed nasal symptom during the peak cedar pollen period more than mono-SLIT with JCP allergens can be a supportive data to validate the efficacy of dual-SLIT with multiple-allergens in poly-sensitized patients.

Some of the adverse events in patients who received dual-SLIT were mouth swelling, throat irritation, oral pruritus, nausea, nasal symptoms, and dermatitis. They were mild (grade 1 as per CTCAEv4) and needed no treatment. It was reported that dual-SLIT with JCP drops or tablets as well as HDM tablets was well tolerated, and that the safety profile was almost the same as in previous studies of mono-SLIT.<sup>14,15</sup>

This study had some limitations, given its retrospective nature, use of a small sample size, baseline characteristics not to be controlled between the two groups, and the differences of JAU doses between JCP drops and tablets. Further randomized controlled studies are needed to prove the efficacy of dual-SLIT with JCP and HDM tablets.

In conclusion, dual-SLIT with JCP and HDM allergens suppressed nasal symptoms during the peak cedar pollen period and in LF in AR patients sensitized to both JCP and HDM allergens. Dual-SLIT with JCP and HDM allergens was more effective in suppressing nasal obstruction symptom during the peak cedar pollen period than mono-SLIT with JCP allergens in bisensitized patients with AR with limitation of baseline characteristics not to be controlled between the two groups. The priming effects of HDM-induced nasal mucosal inflammation exacerbated nasal obstruction during the cedar pollen season in bisensitized patients with Japanese cedar pollinosis in spring. Dual-SLIT with JCP and HDM was more effective than mono-SLIT in patients sensitized to multiple antigens, and well tolerated with mild adverse effects.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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**How to cite this article:** Fujii T, Kitamura Y, Kamimura S, Ishitani K, Takeda N. Efficacy of dual sublingual immunotherapy with Japanese cedar pollen and house dust mite allergens in patients with allergic rhinitis sensitized to multiple allergens. *Laryngoscope Investigative Otolaryngology.* 2022;7(1):36-42. doi:10.1002/lio2.740