

## ORIGINAL

# Effects of sublingual immunotherapy with tablets or drops containing Japanese cedar pollen antigens on nasal symptoms and sleep disturbance in patients with Japanese cedar pollinosis

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**Abstract :** Objective : We examined the effects of SLIT with tablets containing JCP antigens on nasal symptoms and sleep disturbance in patients with Japanese cedar pollinosis during pollen dispersal season. Methods : A total of 128 patients with Japanese cedar pollinosis were categorized into four groups : 19 one-year SLIT with tablets group, 16 two-year SLIT with drops group, 19 antihistamine group, and 74 untreated group. The scores of nasal symptoms and sleep disturbance were evaluated based on the Japanese guidelines for allergic rhinitis and the Athens Insomnia Scale. Results : The scores of nasal symptoms and sleep disturbance at the peak cedar pollen period in the two-year SLIT with drop group and the one-year SLIT with tablets group were significantly lower than those in untreated group. Additionally, these scores were significantly lower in the one-year SLIT with tablets group than those in the antihistamine group. Conclusion : It is suggested that SLIT with JCP tablets improved both nasal symptoms and sleep disturbances at peak pollen period in patients with Japanese cedar pollinosis. SLIT with JCP tablets for one year was more effective than SLIT with JCP drops for two years and prophylactic treatment with antihistamines. *J. Med. Invest.* 69:97-100, February, 2022

**Keywords :** Japanese cedar pollinosis, sublingual immunotherapy, Athens Insomnia Scale, sleep disturbance

## INTRODUCTION

Japanese cedar pollinosis is the most common seasonal allergic rhinitis (AR) in Japan. The aggravation of symptoms, including sneezing, rhinorrhea, nasal obstruction, and itchy eyes during pollen dispersal season not only reduces the quality of life (QOL), but also disturbs sleep at night (1, 2). Reportedly, 38% of patients with Japanese cedar pollinosis complain of sleep disturbance (3).

Allergen-specific immunotherapy provides long-term benefits in patients with AR by altering its natural course of AR. A standardized Japanese cedar pollen (JCP) antigen for sublingual immunotherapy (SLIT) has been available since 2014 in Japan (4). Drops containing JCP antigens are used at a maintenance dose of 2000 Japanese allergy units (JAU), and the efficacy and safety of SLIT with JCP drops in patients with Japanese cedar pollinosis were shown in randomized, double-blind, placebo-controlled studies (5). Moreover, in our previous study, we demonstrated that SLIT with JCP drops improved nasal symptoms, resulting in sleep disturbance relief during the pollen dispersal season in patients with Japanese cedar pollinosis (6).

Recently, tablets containing JCP antigens were also introduced in Japan. JCP tablets are used at a maintenance dose of 5000 JAU/day, which is higher than that of JCP drops. In the present study, we examined the efficacy of SLIT with JCP tablets on nasal symptoms and sleep disturbances during the pollen dispersal season in patients with Japanese cedar pollinosis.

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## METHODS AND METHOD

### Subjects

The present retrospective study was conducted at JA Kochi Hospital, a branch hospital of Tokushima University Hospital. A total of 128 patients with Japanese cedar pollinosis (67 males, 61 females ; mean age : 36.3 ± 20.3 years) were enrolled. All of them had JCP-specific immunoglobulin E levels (Immuno CAP) of class ≥ 2 and had demonstrated obvious symptoms of Japanese cedar pollinosis during at least two previous cedar pollen seasons. They were categorized into four groups : 19 patients (11 men, 8 women ; mean age : 16.7 ± 12.2 years) who received SLIT with JCP tablets for one year as one-year SLIT with tablets group, 16 patients (10 men, 6 women ; mean age : 49.4 ± 14.4 years) who received SLIT with JCP drops for two years as two-years SLIT with drops group, 19 patients (5 men, 14 women ; mean age : 46.7 ± 21.4 years) who received preseasonal prophylactic treatment with antihistamines and continued it during pollen dispersal season as antihistamine group, and 74 patients (41 men, 33 women ; mean age : 39.6 ± 19.0 years) who visited our hospital but did not any treatment during pollen dispersal season as untreated group. This retrospective study was approved by the Committee for Medical Ethics of Tokushima University Hospital (#3547).

### Study drug

Tablets and drops containing JCP (Torii Pharmaceutical Co. Ltd., Tokyo, Japan) were used in this study. The patients in one-year SLIT with tablets group received one tablet daily with the instruction of keeping the tablet under the tongue for 1 min before swallowing without gargling, eating, or drinking for the next 5 min. The dosing schedule comprised an initial 1-week induction period at a dosage of 2000 JAU/day, followed by a maintenance period at a dosage of 5000 JAU/day. The patients in the

two-years SLIT with drop group received JCP liquid drops daily using two kinds of containers with a pump to provide 0.2 ml in one push, at doses of 200 and 2000 JAU/ml and a single-use pouch to deliver 1 ml of 2000 JAU/ml with the instruction of keeping the drops under the tongue for 2 min before swallowing it without gargling, eating, or drinking for the next 5 min. The dosing schedule comprised an initial 2-week induction period at doses that were titrated from 40 JAU/day to 2000 JAU/day, followed by a maintenance period with a dosage of 2000 JAU/day. The patients in the antihistamine group received preseasonal prophylactic treatment with second-generation antihistamines, which was continued during the pollen dispersal season.

Measurement of the JC pollen count

The number of airborne cedar pollen was daily measured 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 hours and was stained with Carbela's solution (7). The number of dyed pollen grains was counted by an optical microscope as the number of pollen grains per cm<sup>2</sup> on the slide.

Evaluation of nasal symptoms and sleep disturbance

The scores of sneezing, rhinorrhea, nasal obstruction and total nasal symptom were evaluated using a 5-point scale of severity, based on the Japanese guidelines for AR (4). Sleep disturbance was also evaluated using the Athens Insomnia Scale (8). The highest scores for the items were analyzed from February 21 (starting of pollen dispersal) to March 31, 2019(end of pollen dispersal).

Statistical analysis

Analysis of variance with post hoc Tukey-Kramer test was used for the statistical analysis. Statistical significance was set at P < 0.05.

RESULTS

In 2019 cedar pollen season, the total amount of dispersed JCP was 8609 grains/cm<sup>2</sup>/year, which was the highest in the last four years and five times higher than the mean amount of 1730 grains/cm<sup>2</sup>/year within four years in Kochi prefecture (Fig. 1).

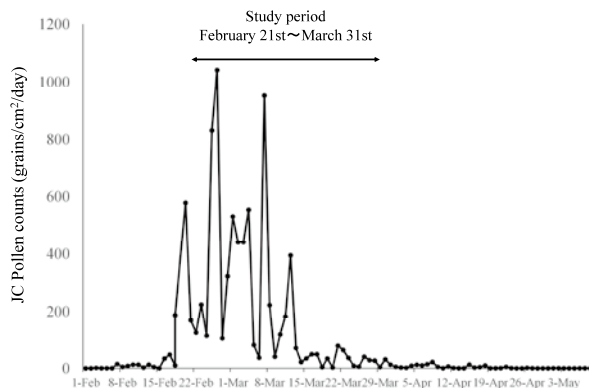


Fig 1. Dispersal of Japanese cedar pollen in 2019. The number of airborne cedar pollen was daily measured using the Durham method as the number of pollen grains per cm<sup>2</sup> on a vaseline-coated glass slide. Horizontal bar : study period.

The scores of sneezing, rhinorrhea, nasal obstruction and total nasal symptoms at the peak cedar pollen period in Japanese pollenosis patients received SLIT with JCP drops for two years (two-year SLIT with drops group) and SLIT with JCP tablets for a year (one-year SLIT with tablets group) were significantly lower than those in Japanese pollenosis patients who did not undergo any treatment (untreated group). The scores of sneezing, nasal obstruction and total nasal symptoms at the peak cedar pollen period in the one-year SLIT with tablets group were significantly lower than those in the antihistamine group (Fig. 2).

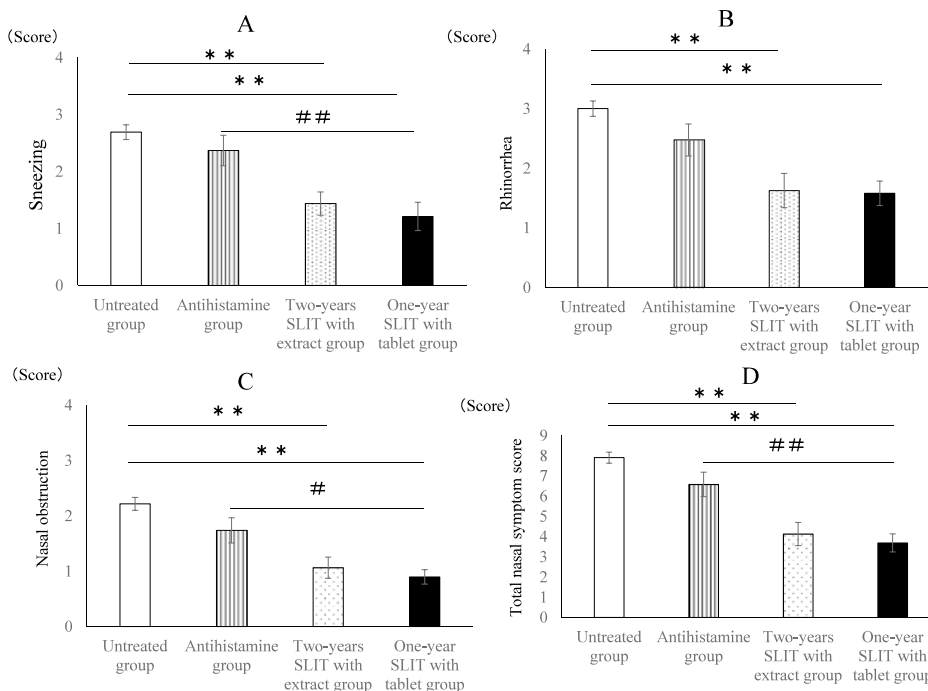


Fig 2. Effect of SLIT with JC pollen tablet on nasal symptoms in patients with Japanese cedar pollenosis. Comparison of sneezing (A), rhinorrhea (B), nasal obstruction (C), and total nasal symptom score (D) in 2019 during JCP dispersal period. Data are presented as mean ± SEM. \*\*p<0.01 vs. untreated group. ##p<0.01, #p<0.05 vs. antihistamine group.

Athens insomnia scale scores at the peak cedar pollen period in two-year SLIT with drops group and one-year SLIT with tablets group were significantly lower than those in the untreated group. Moreover, Athens insomnia scale scores at the peak cedar pollen period in the one-year SLIT with tablets group were significantly lower than those in the antihistamine group (Fig. 3).

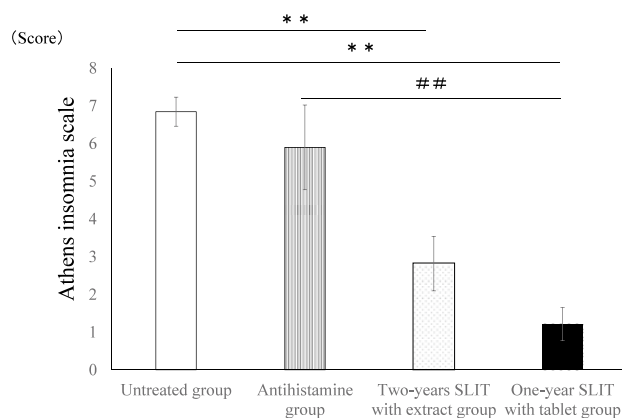


Fig 3. Effect of SLIT with JC pollen tablets on sleep disturbance in patients with Japanese cedar pollinosis. Data are presented as mean ± SEM. \*\*p<0.01 vs. untreated group. ##p<0.01 vs. antihistamine group.

Adverse events in the two-year SLIT with drops group and one-year SLIT with tablets group included mouth edema, throat irritation, rhinorrhea and nausea. All adverse events were mild as grade 1 for CTCAE v4.0 and required no treatment (Table 1).

Table 1. Adverse events of SLIT

	Two-years SLIT with drop group (N=16)	One-year SLIT with tablet group (N=19)
Mouth edema	3	2
Throat irritation	1	4
Rhinorrhea	4	3
Nausea	0	2

## DISCUSSION

In the present study, both the one-year SLIT with tablets group and two-year SLIT with drops group showed improvements in nasal symptoms at peak pollen period as compared to the untreated group. Adverse events were mild and well tolerated. These findings suggest that SLIT with tablets containing JCP antigens was effective and safe for the treatment of Japanese cedar pollinosis, as well as SLIT with JCP drops. A double-blind randomized clinical trial showed that, as compared to SLIT with placebo, SLIT with JCP drops for one and two years suppressed seasonal nasal symptoms in patients with Japanese cedar pollinosis (5). Furthermore, another double-blind randomized clinical trial also showed that SLIT with JCP tablets for two and three years improved seasonal nasal and ocular symptoms in patients with Japanese cedar pollinosis in a treatment duration-dependent manner compared to SLIT with placebo (9). Any serious adverse events were not reported during these trials.

In the present study, nasal symptoms showed improvement at peak pollen period in the one-year SLIT with tablets group but

not two-year SLIT with drop group as compared with the antihistamine group. These findings suggest that SLIT was more effective than antihistamines for the treatment of Japanese pollinosis. Long-term SLIT with JCP drops has been reported to better suppress seasonal nasal symptoms than antihistamines in patients with Japanese cedar pollinosis (10). In addition, a pooled analysis showed that the efficacy of SLIT with tablets containing grass and ragweed antigens was numerically greater than that with antihistamines (11). Antihistamine reduces histamine signaling by their blocking effect against histamine on histamine H<sub>1</sub> receptors, resulting in decreased nasal allergy symptoms in patients with AR (12-14). On the other hand, SLIT alters the patient's immune profile, including the immune response toward the production of Th1 and regulatory T lymphocytes and the induction of isotopic class switch in B lymphocytes to IgG4 with a reduction in IgE levels (15-17). Therefore, it is suggested that the altered immune profile following SLIT has a greater impact on the treatment of AR than symptomatic treatment with antihistamines.

The present findings suggested that SLIT with JCP tablets was more effective than SLIT with JCP drops for the treatment of Japanese pollinosis. It was reported that the efficacy of SLIT with JCP tablets for one year was similar or greater than that of SLIT with JCP drops for two years in patients with Japanese cedar pollinosis (9). SLIT with JCP tablets and drops were administered at the maintenance doses of 5000 and 2000 JAU/day respectively. Because it was reported that SLIT with JCP antigens for a year suppressed nasal symptoms at the peak pollen period in a dose-dependent manner from 2000 to 5000 JAU/day (18), it is suggested that the dose-dependent efficacy of SLIT is responsible for the advantage of SLIT with JCP tablets over JCP drops.

In the present study, Athens insomnia scale score of sleep disturbance at the peak pollen period in one-year SLIT with tablets group was lower than those in the antihistamine and untreated groups. It has been reported that allergic rhinitis leads to disturbed sleep at night (2) and that about 40% of patients with Japanese cedar pollinosis complained of sleep disturbance (3). Additionally, It has been reported that intranasal corticosteroids and leukotriene receptor antagonists improved not only nasal symptoms but also sleep disturbance, leading to improvement in the QOL of patients with AR (19-21). We reported that SLIT with JCP drops decreased nasal symptoms, leading to improvement in AR-related sleep disturbances (6). Nasal obstruction disturbs sleep in patients with AR (20, 22). Since nasal symptoms, including nasal obstruction improved in the one-year SLIT with tablets group in the present study, it is suggested that SLIT with JCP tablets relieves nasal obstruction, resulting in the improvement of sleep disturbance during the pollen season.

This study was limited by its non-randomized placebo-controlled study design, retrospective test, little intervention for the registration of 128 people. In addition, this study was conducted only in Japan because Japanese cedar pollinosis was an unique allergic rhinitis in Japan, thus requiring further randomized controlled studies to prove the effect of SLIT with JCP.

## CONCLUSION

In the present study, the effects of SLIT with tablets containing JCP antigens on allergic rhinitis symptoms and sleep disturbances were examined in patients with Japanese cedar pollinosis during the pollen dispersal season. SLIT with JCP tablets for one year improved both nasal symptoms and sleep disturbance at peak pollen period and was more effective than SLIT with JCP drops for two years, probably because of the

dose-dependent efficacy of SLIT. SLIT with JC tablets for one year was also more effective than prophylactic treatment with antihistamines, probably because of the immune profile-altering ability of SLIT.

## CONFLICT OF INTERES

The authors have no conflicts of interest to declare.

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