ORIGINAL

Comparison of the efficacy of sublingual immunotherapy and prophylactic treatment with antihistamines on allergic rhinitis symptoms and quality of life in small and large Japanese cedar pollen dispersal years

Tatsuya Fujii[1,2], Seiichiro Kamimura[2], Keisuke Ishitani[2], and Yoshiaki Kitamura[2]

[1]Department of Otolaryngology, JA Kochi Hospital, Kochi, Japan, [2]Department of Otolaryngology, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan

Abstract : Background : It remains to be elucidated that the differences in treatment effects on allergic rhinitis (AR) symptoms and quality of life (QOL) in patients with Japanese cedar (JC) pollinosis during different pollen dispersal seasons. Objectives : We compared the effects of sublingual immunotherapy (SLIT) with JC pollen tablets and prophylactic treatment with antihistamines on AR symptoms and QOL during different JC pollen dispersal seasons. Material and Methods : 106 and 129 patients with JC pollinosis were enrolled during the small and large JC pollen dispersal seasons, respectively. They were categorized into the SLIT, antihistamine, and untreated groups. AR symptoms and QOL scores were evaluated. Results : The SLIT group showed significant improvement in all AR symptoms and QOL scores compared with the untreated group during both the small and large pollen dispersal seasons. The antihistamine group showed significantly improved nasal symptoms and higher QOL scores than the untreated group during the small pollen dispersal season, but it did not show any improved QOL scores, during the large pollen dispersal season. Conclusions : These findings suggested that JC pollen SLIT was more effective in suppressing AR symptoms than prophylactic treatment with antihistamines, resulting in improved QOL during the large JC pollen dispersal season. J. Med. Invest. 73 : 55-61, February, 2026

Keywords **:** *Japanese cedar pollinosis, sublingual immunotherapy, quality of life, prophylactic treatment, Japanese cedar pollen account*

INTRODUCTION

JC pollinosis is the most common form of seasonal allergic rhinitis (AR) in Japan (1). AR is not a life-threatening disease, even when severe, however, it greatly affects daily activity, work productivity, learning, sleep, and QOL. Therefore, AR therapy should not only suppress AR symptoms but also improve QOL. Allergen-specific immunotherapy provides long-term benefits in patients with AR by altering the natural course of AR (2). A standardized JC pollen antigen for sublingual immunotherapy has been available since 2014 in Japan (3). Moreover, tablets containing JC pollen antigens, even suitable for children aged > 5 years, were introduced in Japan in 2018 (4, 5).

Nasal and ocular symptoms in patients with JC pollinosis worsen with increasing JC pollen dispersal (6). Therefore, it is possible that treatment effects differ when the JC pollen dispersal accounts are different. We demonstrated that JC pollen SLIT improved both nasal symptoms and sleep disturbances during the peak pollen period, and was more effective than prophylactic antihistamine treatment (7, 8). However, few studies have investigated the differences in treatment effects on AR symptoms and QOL in patients with JC pollinosis during different JC pollen dispersal seasons. Therefore, we examined the effects of JC pollen SLIT and prophylactic antihistamine treatment on AR symptoms and QOL during the small and large JC pollen dispersal seasons in patients with JC pollinosis.

MATERIALS AND METHODS

Participants

This retrospective study was conducted at the JA Kochi Hospital, a branch of Tokushima University Hospital. A total of 106 patients with JC pollinosis (54 males, 52 females ; mean age : 35.0 ± 22.7 years) were enrolled in 2020, a small JC pollen dispersal year. Subsequently, a total of 129 patients with JC pollinosis (65 males, 64 females ; mean age : 28.6 ± 20.3 years) were enrolled in 2021, a large cedar pollen dispersal year. In the small JC dispersal year, participants were categorized into three groups : 54 patients (36 men, 18 women ; mean age : 23.9 ± 20.2 years) who received SLIT with JCP tablets into the SLIT group, 20 patients (6 men, 14 women ; mean age : 46.9 ± 17.1 years) who received preseasonal prophylactic treatment with antihistamines that was continued during the pollen dispersal season into the antihistamine group and 32 patients (12 men, 20 women ; mean age : 46.2 ± 21.0 years) who visited our hospital but did not receive any treatment into the untreated group. In the large JC pollen year, the groups were : 70 patients (45 men, 25 women ; mean age : 20.1 ± 17.6 years) into the SLIT group, 23 patients (7 men, 16 women ; mean age : 50.0 ± 17.0 years) into the antihistamine group and 36 patients (13 men, 23 women ; mean age : 31.4 ± 16.0 years) into the untreated group. All patients had JCP-specific immunoglobulin E levels class ≥2 (Immuno CAP or Multiple Allergen Simultaneous Test 36) and had demonstrated

Abbreviations :
sublingual immunotherapy, SLIT ; Japanese cedar, JC ; allergic rhinitis, AR ; quality of life, QOL ; Japanese Rhinoconjunctivitis Quality of Life Questionnaire, JRQLQ

Received for publication May 18, 2025 ; accepted September 24, 2025.

Address correspondence and reprint requests to Yoshiaki Kitamura, M.D., Ph.D., Department of Otolaryngology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto, Tokushima 770-8503, Japan and Fax : +81-88-633-7170. E-mail : ykitamura@tokushima-u.ac.jp (YK)

obvious symptoms of JC pollinosis during at least two previous cedar pollen seasons. Patients background including gender, age, JC pollen-specific IgE class value, other antigen sensitization, presence of other allergic complications, and duration of JCP SLIT were shown for each group separately in Table1. This retrospective study was approved by the Committee for Medical Ethics of Tokushima University Hospital (# 3789-1).

Study drug

Tablets containing JCP (Torii Pharmaceutical Co. Ltd., Tokyo, Japan) were used in this study. The SLIT group received one tablet daily and instructed to keep the tablet under their tongue for 1 min and swallow without gargling, eating, or drinking for the next 5 min. The dosing schedule comprised an initial 1-week induction period at a dosage of 2,000 JAU/day, followed by a maintenance period at a dosage of 5,000 JAU/day. 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 grains was measured daily using the Durham method at the JA Kochi Hospital in Kochi Prefecture during the pollen dispersal season. A baseline-coated glass slide was placed on a Durham gravity sampler for 24 h and then stained with Carbela's solution (9). The number of dyed pollen grains was counted using an optical microscope as the number of pollen grains per cm^2 on the slide.

Evaluation of nasal symptoms and QOL

Sneezing, rhinorrhea, nasal obstruction, itchy eyes, total nasal and ocular symptoms and medication scores (TNOSMS), and QOL were evaluated using a 5-point scale of the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) which asked the highest scores in the past 2 weeks (10). All patients visited our hospital 2-3 times including the peak pollen period, from late February to middle of March and the highest scores for these items were obtained from February 21 (start of pollen dispersal) to March 31 (end of pollen dispersal), in 2020 and 2021. In the antihistamine group, antihistamines were prescribed at the time of their first visit as prophylactic treatment before the peak pollen period. In the untreated group, these patients were evaluated for their symptoms at the time of their first visit during the peak pollen period. The following drugs were administered as needed depending on their symptom profiles : oral antihistamine, ocular antihistamine, leukotriene antagonists, and nasal steroids. Medication scores were determined according to the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2020 Edition, and patients reported both medication adherence and rescue medication use in the past 2 weeks at the time of the interview.

Statistical analysis

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

RESULTS

During the 2020 and 2021 JC pollen seasons, the total amount of dispersed JC pollen was 1358 and 4283 grains/cm^2/year, respectively. Because the mean JC pollen dispersal amount within seven years was 2952 grains/cm^2/year, the JC pollen dispersal amount was small in 2020, and large in 2021 (Fig. 1).

In 2020, the small JC pollen dispersal year, all AR symptom scores for rhinorrhea, sneezing, nasal obstruction, and itchy eyes in the SLIT group were significantly lower than the untreated group. In contrast, sneezing and nasal obstruction scores in the antihistamine group were significantly lower than the untreated group (Fig. 2). In 2021, the large JC pollen dispersal year, all symptom scores for rhinorrhea, sneezing, nasal obstruction, and itchy eyes in the SLIT group were significantly lower than the untreated group. Rhinorrhea, sneezing and nasal obstruction scores in the antihistamine group were significantly lower than the untreated group. Moreover, scores for sneezing and

Table 1.

	In 2020 (N = 106)			In 2021 (N = 129)		
	Untreated group N = 32	Antihistamine group N = 20	SLIT group N = 54	Untreated group N = 36	Antihistamine group N = 23	SLIT group N = 70
Age (mean±SD)	46.2 ± 21.0	46.9 ± 17.1	23.9 ± 20.2	31.4 ± 16.0	50.0 ± 17.0	20.1 ± 17.6
Gender (male : female)	12 : 20	6 : 14	54 : 52	13 : 23	7 : 16	65 : 64
JC pollen-specific IgE class value	4.0 ± 1.5	3.7 ± 2.1	4.6 ± 1.3	4.3 ± 1.3	3.0 ± 0.6	4.4 ± 1.5
Other antigen sensitization						
Cypress	8	5	25	8	5	27
Housedust mite	9	6	31	12	8	43
Cat	5	3	17	5	3	19
Dog	1	1	4	2	1	8
Grass	2	2	8	4	2	14
Ragweed	1	1	4	2	1	8
Other allergic complications						
Asthma	7	1	6	5	4	10
Atopic dermatitis	0	0	2	0	2	1
Duration of JCP SLIT						
1 year	n/a	n/a	42	n/a	n/a	25
2 year	n/a	n/a	12	n/a	n/a	33
3 year	n/a	n/a	0	n/a	n/a	12

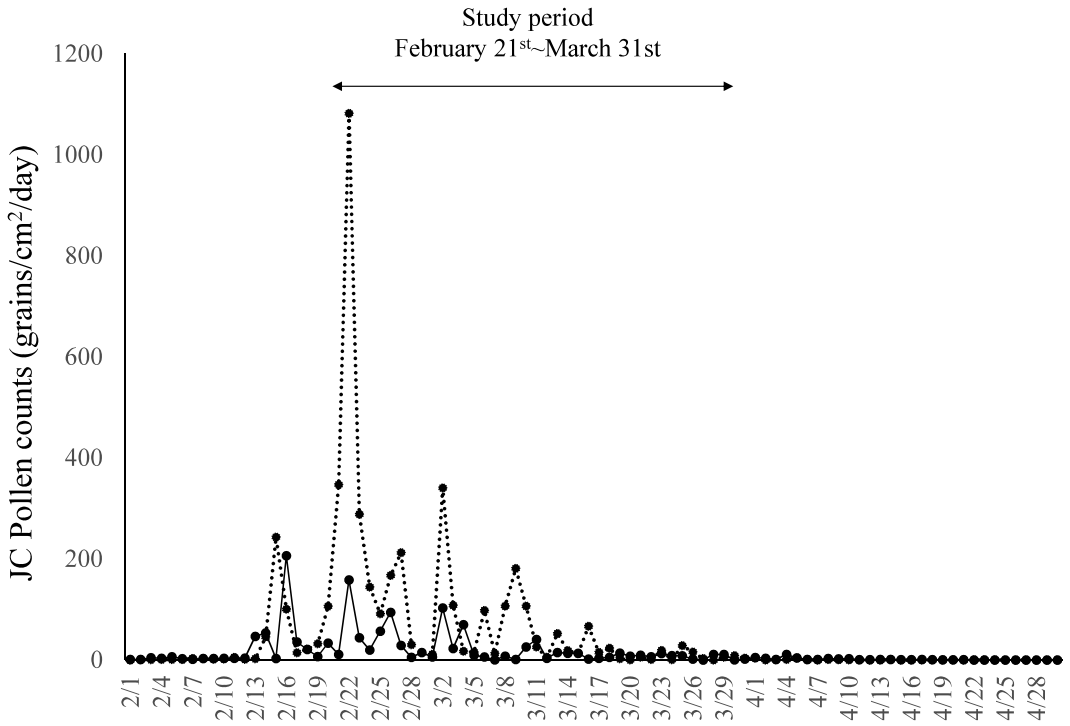

Figure 1. Dispersal of Japanese cedar pollen in 2020 and 2021. The number of airborne cedar pollen grains was measured daily, as pollen particles per cm^2 on Vaseline-coated glass slides was measured daily using the Durham method. The numbers of airborne cedar pollen particles in 2020 and 2021 are represented by solid and dotted lines, respectively. Horizontal bar : Study period.

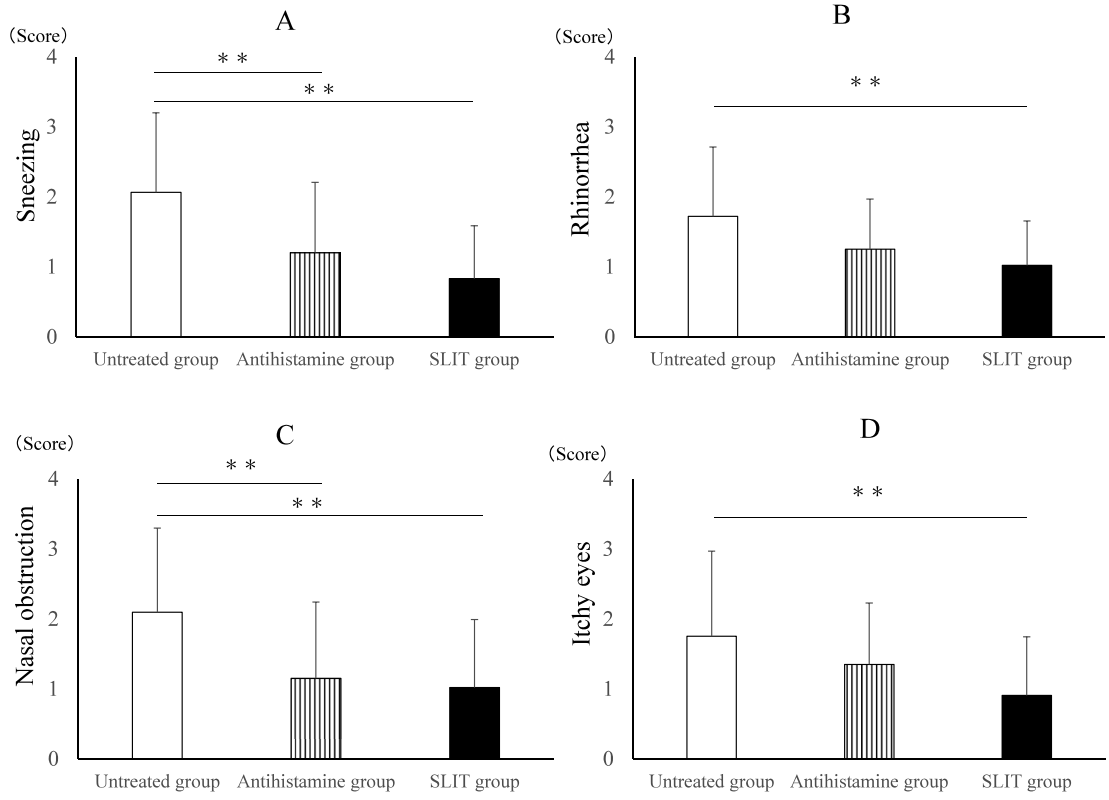

Figure 2. Effects of SLIT with Japanese cedar (JC) pollen tablets on nasal and ocular symptoms in patients with JC pollinosis in a small cedar pollen dispersal year. Comparison of sneezing (A), rhinorrhea (B), nasal obstruction (C), and itchy eyes (D) in 2020 during the small JCP dispersal period. Data are presented as mean ± SD. **P<0.01, *P<0.05 vs. untreated group.

itchy eyes in the SLIT group were significantly lower than the antihistamine group (Fig. 3). In addition, the TNOSMS in both antihistamine group and SLIT group were significantly lower than untreated group in the small and large JC pollen dispersal year. Furthermore, the TNOSMS in the SLIT group were significantly lower than antihistamine group in the large JC pollen dispersal year (Fig. 4).

In the small JC pollen dispersal year, all QOL scores for usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional function in the SLIT group were significantly lower than the untreated group. The QOL scores for usual daily activities, outdoor activities, social functioning, general physical problems, and emotional function, but not sleep problems, in the antihistamine group were significantly lower than the untreated group. Moreover, the QOL scores for sleep problems in the SLIT group were significantly lower than the antihistamine group (Fig. 5). In the large JC pollen dispersal year, all QOL scores in the SLIT group were significantly lower than the untreated group, but there was no significance in any of the QOL scores between the antihistamine group and the untreated group (Fig. 6).

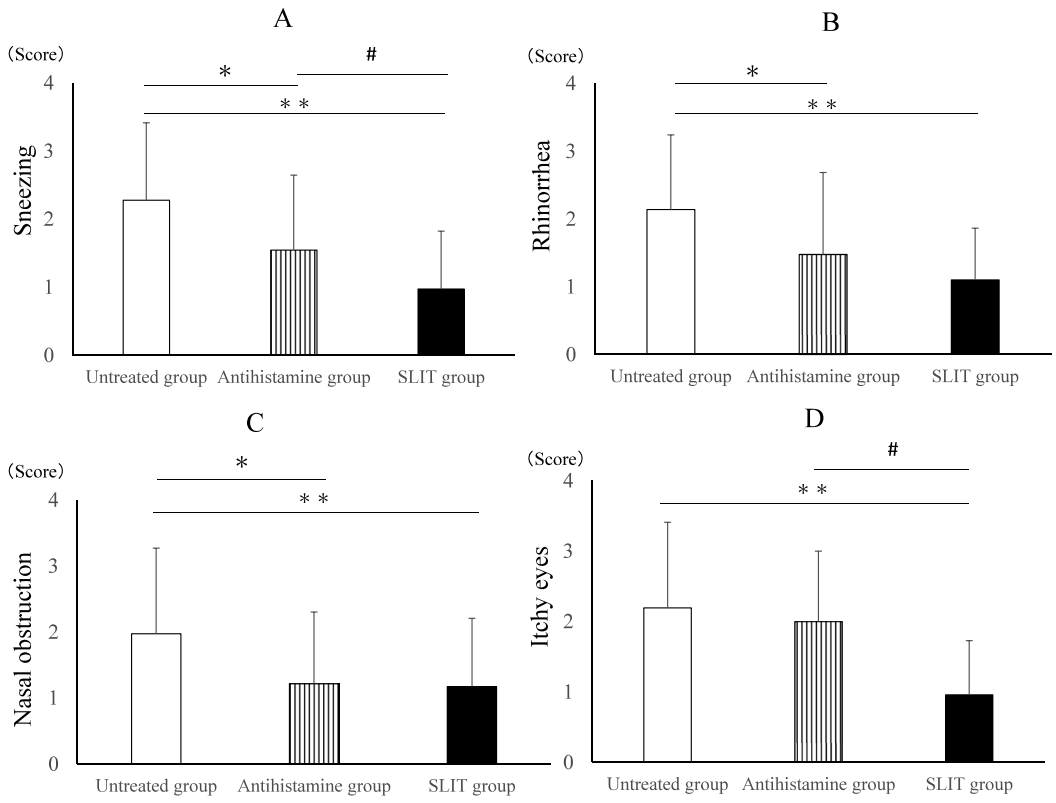

Figure 3. Effects of SLIT with Japanese cedar (JC) pollen tablets on nasal and ocular symptoms in patients with JC pollinosis in a large cedar pollen dispersal year. Comparison of sneezing (A), rhinorrhea (B), nasal obstruction (C), and itchy eyes (D) in 2021 during the large JCP dispersal period. Data are presented as mean ± SD. **P<0.01, *P<0.05 vs. untreated group. #P<0.05 vs. antihistamine group.

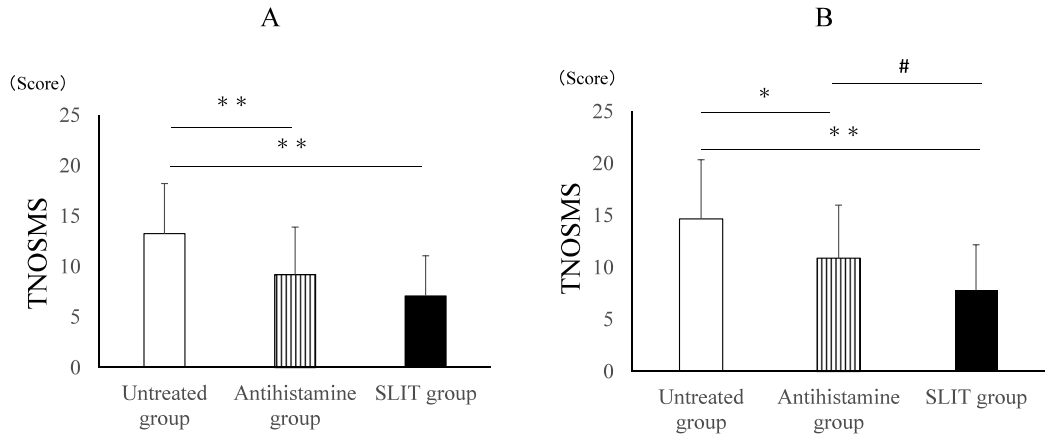

Figure 4. Effects of SLIT with Japanese cedar (JC) pollen tablets on total nasal and ocular symptoms and medication scores (TNOSMS) in patients with JC pollinosis in the small and large cedar pollen dispersal year. A : small JC pollen dispersal year in 2020 B : large JC pollen dispersal year in 2021. Data are presented as mean ± SD. **P<0.01, *P<0.05 vs. untreated group. #P<0.05 vs. antihistamine group.

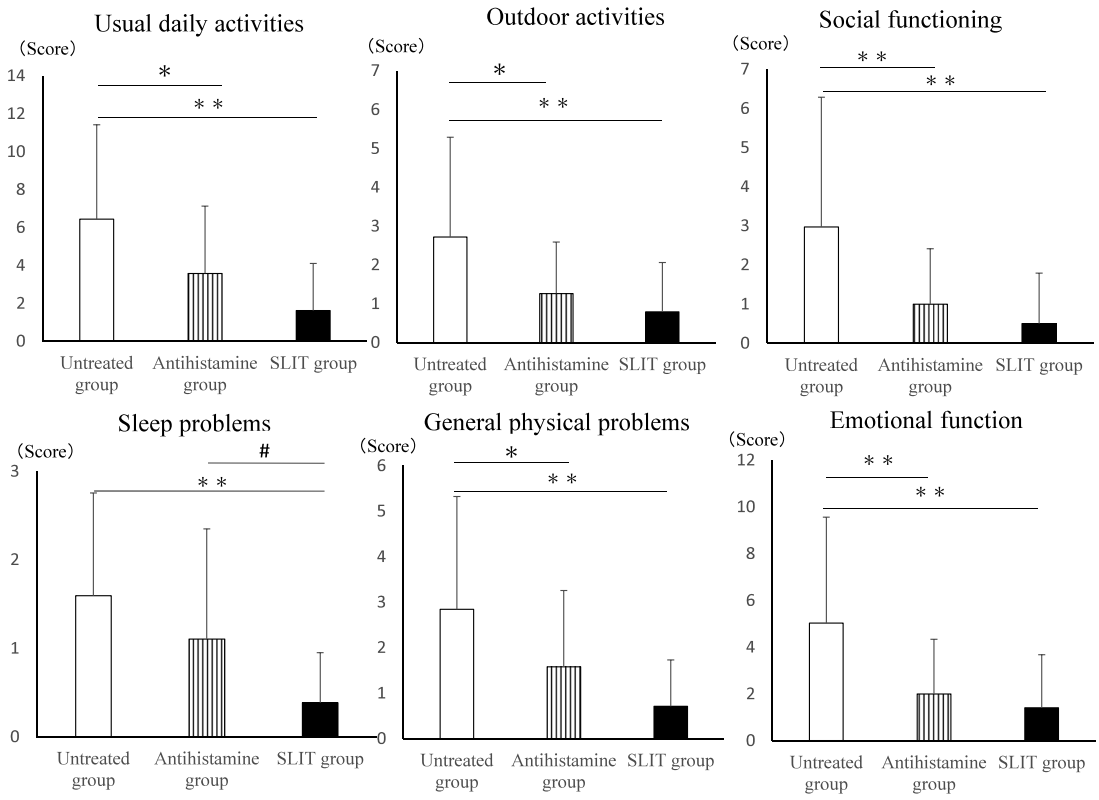

Figure 5. Effects of SLIT with JC pollen tablets on quality of life (QOL) in patients with Japanese cedar pollinosis during a small cedar pollen dispersal year (2020). Comparison of usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional functions during the JCP dispersal period. Data are presented as mean ± SD. **P<0.01, *P<0.05 vs. untreated group. #P<0.05 vs. antihistamine group.

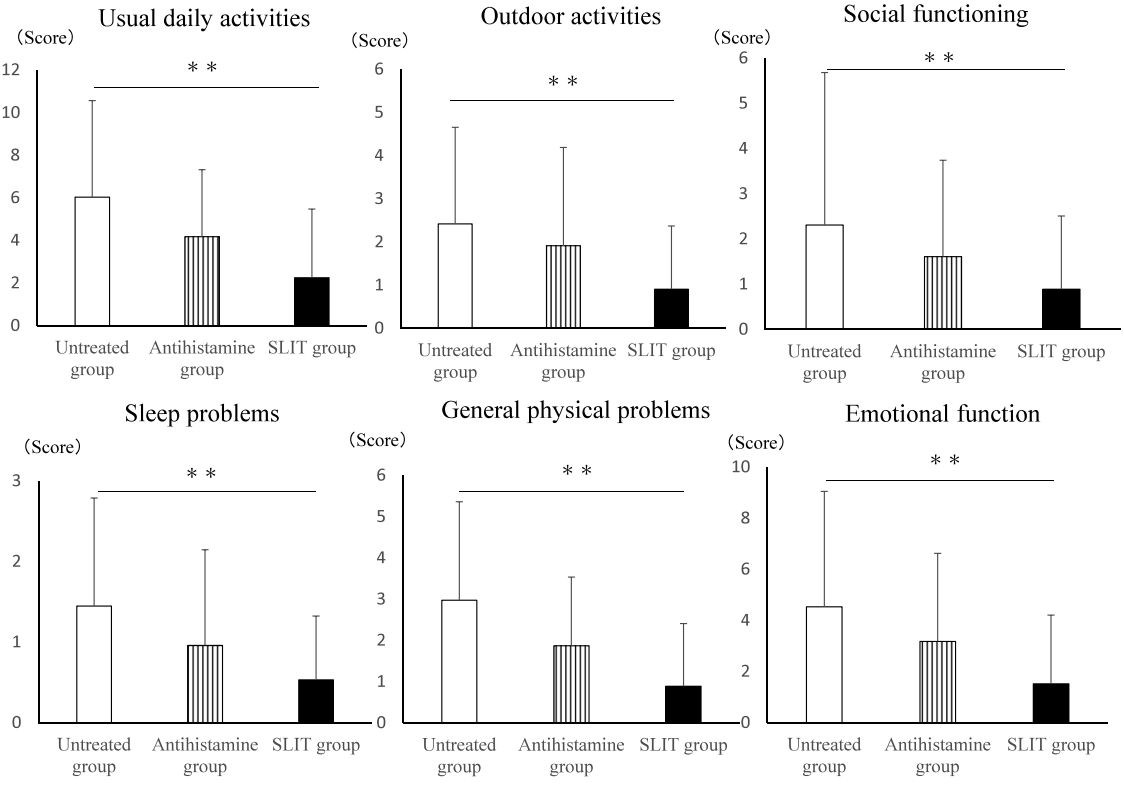

Figure 6. Effects of SLIT with JC pollen tablets on quality of life (QOL) in patients with Japanese cedar pollinosis during a large cedar pollen dispersal year (2021). Comparison of usual daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional functions during the JCP dispersal period. Data are presented as mean ± SD. **P<0.01 vs. untreated group.

DISCUSSION

In this study, all scores for rhinorrhea, sneezing, nasal obstruction, and itchy eyes in the SLIT group were significantly lower than the untreated group, regardless of the amount of JC pollen dispersed. Contrastingly, scores for sneezing and nasal obstruction in the antihistamine group were significantly lower than the untreated group in the small JC pollen dispersal year, and scores for rhinorrhea, sneezing, and nasal obstruction were significantly lower than the untreated group in the large JC pollen dispersal year. Meanwhile, TNOSMS in both SLIT group and antihistamine group were significantly lower than untreated group in the small and large JC pollen dispersal year. A previous randomized, double-blind, placebo-controlled study reported that JC pollen SLIT tablets significantly improved nasal and ocular symptoms compared with the placebo group in the JC pollen dispersal season (4, 5). Additionally, prophylactic treatment with oral antihistamines (olopatadine) significantly improved nasal symptoms and QOL compared with the placebo group during the peak of JC pollen dispersal season (11). It has been reported that the mechanism of SLIT activity is an immune response toward the production of Th1 and regulatory T lymphocytes and the induction of an isotopic class switch of B lymphocytes to IgG4, with a reduction in IgE levels (12-14). On the other hand, the mechanism of prophylactic treatment with antihistamines is reducing histamine signaling by their blocking effect against histamine on the histamine H_1 receptors (H1R) and suppressing the upregulation of H1R, IL-4, and IL-5 expression, resulting in decreased nasal allergy symptoms in patients with AR (15-18). Moreover, Durham *et al*. suggested that in seasonal allergy trials with grass SLIT-tablets, the treatment effect was highly dependent on pollen exposure, with the effect being greater with higher pollen exposure, and grass SLIT tablets reduced appropriately 20% of total rhinoconjunctivitis symptoms and medication scores compared to placebo even in the small pollen dispersal year (19). It has also been reported that the treatment effects of grass SLIT on nasal symptoms increase as pollen dispersal increases (20). These findings suggest that JC pollen SLIT improved nasal and ocular symptoms by altering immune profiles regardless of JC pollen dispersal amount, however, the treatment effects of prophylactic treatment with antihistamines on nasal and ocular symptoms were limited in the large JC pollen dispersal year.

In this study, the SLIT group significantly improved scores for sneezing and itchy eyes, and TNOSMS compared with the antihistamine group in the large JC pollen dispersal year even though AR symptoms in all three groups worsened. It is suggested that the difference of efficacy between these treatments becomes clinically apparent in the large JC pollen dispersal year because AR symptoms in each group worsened differently. A pooled analysis showed that the efficacy of SLIT with tablets containing grass and ragweed antigens was greater than that with antihistamines (21). Moreover, we demonstrated that SLIT with JC pollen tablets improved both nasal symptoms and sleep disturbance during the peak pollen period and was more effective than prophylactic treatment with antihistamines, especially in large JC pollen dispersal year with 8609 grains/cm^2/year in 2019 (8). These findings suggest that JC pollen SLIT is more effective on nasal symptoms than prophylactic treatment with antihistamines during the large JC pollen dispersal years.

In this study, the SLIT group had significant improvement in all QOL scores compared with the untreated group, regardless of JC pollen dispersal accounts. Contrastingly, while the antihistamine group did show significant improvement in many QOL scores compared with the untreated group in the small JC pollen dispersal year, there was no improvement in any of the QOL scores in the large JC pollen dispersal year. A previous randomized, double-blind, placebo-controlled study reported that JC pollen SLIT tablets significantly improved QOL scores compared to the placebo group in the second and third JC pollen dispersal seasons (5). Although it has been reported that prophylactic treatment with antihistamines also improved QOL scores compared with the placebo group during the JC pollen dispersal season (11), in this study, the SLIT group significantly improved scores for sneezing and itchy eyes compared with the antihistamine group in the large JC pollen dispersal year. These findings suggest that SLIT has a greater treatment effect on AR symptoms than prophylactic treatment with antihistamines, resulting in improved QOL in the large JC pollen dispersal year.

This study was limited by its non-randomized, placebo-controlled design, retrospective nature, and minimal intervention for the registration of 235 patients. Additionally, patients in 2021 were significantly younger than those in 2020 and we could not evaluate the impact of cypress pollen on JC pollinosis patients who visited at the end of March. The duration of JC pollen SLIT differed between years with low and high JC pollen dispersal. In the small JC pollen dispersal year, the majority of the patients received SLIT for only one year, whereas in the large JC pollen dispersal year, over half of the patients continued SLIT therapy for more than two years. This discrepancy in treatment duration could represent a potential confounding factor and may have influenced the observed outcomes.

CONCLUSION

SLIT with JC pollen tablets significantly improved nasal and ocular symptoms and QOL scores regardless of JC pollen dispersal accounts. However, prophylactic treatment with antihistamines did not improve QOL scores in the large JC pollen dispersal year. This suggests that SLIT is more effective in suppressing AR symptoms than prophylactic treatment, leading to an improvement in QOL even during the large JC pollen dispersal season.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

This study was supported by Support Center for Advanced Medical Sciences, Institute of Biomedical Sciences, Tokushima University Graduate School.

AUTHOR CONTRIBUTIONS

TF designed the study and wrote the manuscript. SK, KI, and YK contributed to interpretation of results and data collection. YK critically revised the manuscript. All authors read and approved the final manuscript.

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