Efficacy of Japanese cedar pollen sublingual immunotherapy tablets for Japanese cypress pollinosis

Tomoya Kurokawa, MD, PhD,[a,b] Syuji Yonekura, MD, PhD,[a] Minoru Gotoh, MD, PhD,[c] Mitsuhiro Okano, MD, PhD,[d] Yuriko Maekawa, BSc,[e] Kimihiro Okubo, MD, PhD,[c] and Yoshitaka Okamoto, MD, PhD[a,f] *Chiba and Tokyo, Japan*

Background: We previously demonstrated the efficacy of Japanese cedar (JC) pollen sublingual immunotherapy (SLIT) tablets for treating seasonal allergic rhinitis in a clinical trial (trial no. 206-2-1) that covered 5 pollen dispersal seasons from 2015 to 2019.

Objective: Our aim was to perform *post hoc* analysis of the 206-2-1 trial data to evaluate the efficacy of JC pollen SLIT tablets for patients with rhinitis induced by pollen from Japanese cypress (JCY), a related Cupressaceae species that has a pollen dispersal season overlapping with that of JC.

Methods: Data were analyzed for 240 patients who received placebo during the first pollen dispersal season in 2015, were then rerandomized to receive JC SLIT tablets (the PA group) or placebo (the PP group) for 18 months (the 2016 and 2017 dispersal seasons), and were observed untreated for 2 years (the 2018 and 2019 dispersal seasons). The PA and PP groups were assigned to "high" and "low" subgroups if their rhinitis symptoms were exacerbated/did not change or decreased, respectively, during the peak JCY pollen dispersal period in 2015. The mean total nasal symptom and medication scores and other outcomes were compared for the high-PP, high-PA, low-PP, and low-PA groups during the 2016 to 2019 peak JCY pollen dispersal periods.

Results: The mean total nasal symptom and medication scores were significantly lower for the high-PA and low-PA groups than for the corresponding PP groups over the 4 years of treatment and observation. JCY pollen–specific IgE levels increased in both PA groups.

Conclusion: JC pollen SLIT tablets effectively suppressed JCY pollinosis symptoms, supporting the clinical relevance of immunologic cross-reactivity between JC and JCY allergens. (J Allergy Clin Immunol Global 2023;2:100075.)

Key words: *Allergy immunotherapy, sublingual immunotherapy, disease modification, sustained efficacy, Japanese cedar, Japanese cypress, allergic rhinitis, conjunctivitis, cross-reactivity, homologous*

The prevalence of Japanese cedar (JC) pollinosis in Japan has increased markedly in recent years.[1,2] Approximately 70% of patients with JC pollinosis are also allergic to Japanese cypress (JCY) pollen[1]; consequently, patients with combined JC and JCY pollinosis experience severe symptoms from February to May, which encompasses the JC pollen dispersal season from February to April and the JCY pollen dispersal season from March to May.[3] JC and JCY are members of the Cupressaceae family of conifers, and their allergens share high amino acid sequence homology and other properties.[4] For example, the amino acid homologies of the major pollen allergens of JC (*Cryptomeria japonica*) and JCY (*Chamaecyparis obtusa*) have been reported to be 80% between *Cryptomeria japonica* (Cry j) 1 and *Chamaecyparis obtusa* (Cha o) 1, 74% between Cry j 2 and Cha o 2, and 85% between Cry j 4 and Cha o 3.[5] As a result, the allergens are also antigenically similar and elicit extensively cross-reactive humoral immunity, including immunoglobulin E (IgE).[4,6]

The current guidelines for allergen immunotherapy state that a single allergen or a mixture of homologous allergens derived from the same biologic families can be administered to patients sensitized to multiple taxonomically related homologous allergens.[7] Allergy immunotherapy with birch pollen extract was recently shown to be effective for the treatment of allergies to pollen from birch-homologous trees, such as hazel and oak.[8] Birch pollen is considered to be a representative source of allergens of the Fagales order of trees on the basis of sequence and structure.[8]

JC pollen sublingual immunotherapy (SLIT) tablets containing the major JC allergens, such as Cry j 1 and Cry j 2, were approved for treatment of JC pollinosis in Japan in 2017. Given the high protein sequence homology between the major JC and JCY pollen allergens, it is reasonable to consider that JC pollen SLIT agents may be an effective treatment for rhinitis symptoms caused by JCY pollen; however, the results to date have been controversial.

From [a]the Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University; [b]the Clinical Research Center, Chiba University Hospital; [c]the Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo; [d]the Department of Otorhinolaryngology, International University of Health and Welfare, Chiba; [e]the Department of Medical Affairs, Torii Pharmaceutical Co, Ltd, Tokyo; and [f]the Chiba Rousai Hospital.

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Corresponding author: Yuriko Maekawa, BSc, Medical Affairs Department, Torii Pharmaceutical Co, Ltd, Tokyo, Japan. E-mail: yuriko.maekawa@torii.co.jp.

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Abbreviations used
ADR: Adverse drug reaction
AE: Adverse event
Cha O: *Chamaecyparis obtusa*
Cry j: *Cryptomeria japonica*
FAS: Full analysis set
JAU: Japanese allergy unit
JC: Japanese cedar
JCY: Japanese cypress
LS: Least squares
PA: Placebo-to-active
PP: Placebo-to-placebo
SLIT: Sublingual immunotherapy
SQ: Standardized quality
TNSMS: Total nasal symptom and medication score
TOSMS: Total ocular symptom and medication score

For example, in a survey of patients (180 cases) being treated with JC pollen SLIT drops in actual clinical practice, both effective and ineffective cases of SLIT during the JCY pollen season were reported, even among cases in which the therapy was effective during the JC pollen season.[9] We also examined the efficacy of JC pollen SLIT tablets for the JC and/or JCY pollen dispersal period using the 206-2-1 study (JapicCTI no. 142579); however, we have not been able to analyze the tablets' efficacy in a patient group with specific JCY pollen allergy symptoms.[10]

The purpose of the present *post hoc* analysis was to evaluate the effect of JC pollen SLIT tablets specifically on allergy symptoms occurring during the peak periods of JCY pollen dispersal in 2016 to 2019 in patients segregated on the basis of the severity of their JCY pollen allergy symptoms.

METHODS

Trial design

The 206-2-1 trial was a randomized, double-blind, placebo-controlled field trial (JapcCTI-142579) of JC pollen SLIT tablets for patients with JC pollinosis (>1000 participants aged 5-64 years); the details and primary results of this trial have been reported previously.[11-13] Briefly, the trial consisted of 3 phases: a dose-finding period (encompassing the first overlapping JC/JCY pollen dispersal season in 2015), an 18-month treatment period with placebo and 5000 Japanese allergy units (JAU) of JC pollen SLIT tablets (encompassing the second and third pollen dispersal seasons in 2016 and 2017), and a 2-year observational period (encompassing the fourth and fifth pollen dispersal seasons in 2018 and 2019) (Fig 1).

Patient subgroups

Subject enrollment was restricted to residents of Tokyo and its suburbs to minimize variations in natural exposure to JC pollen. The inclusion criteria have been reported previously[11-13] and are available in this article's Supplementary Methods (available in the Online Repository at www.jaci-global.org). The trial complied with Good Clinical Practice guidelines and the Declaration of Helsinki, and it was approved by the institutional review board at each clinical site. Written informed consent was obtained from all subjects and legal representatives of underage subjects.

For this *post hoc* analysis, data were obtained for 240 patients who received placebo during the dose-finding period and were then rerandomized to either placebo (the placebo-to-placebo [PP] group, the members of which were rerandomized to receive placebo [n = 159]) or JC pollen SLIT tablets (the placebo-to-active [PA] group, the members of which were rerandomized to receive 5000 JAU [n = 81]) for the 18-month treatment period. Follow-up efficacy and safety evaluations were continued for 2 years for both groups. Patients in the PA and PP groups were further assigned to 2 subgroups based on their rhinitis symptoms (measured as total nasal symptom and medication scores [TNSMSs]) during the 7-day peak JCY pollen dispersal period in 2015 (March 27-April 2 [see Table E2 in the Online Repository at www.jaci-global.org]) compared with their TNSMSs for the preceding 7 days. Patients whose scores increased or did not change during the peak week were assigned to the "high" groups and those whose scores decreased were assigned to the "low" groups, thus resulting in high-PP, high-PA, low-PP, and low-PA groups.

Study drug

Patients were administered a fast-dissolving lyophilized SLIT tablet (manufactured by ALK-Abelló, Hørsholm, Denmark) containing 5000 JAU of the major JC allergen Cry j 1. In 1996, the Japanese Society of Allergology Task Force (1996) defined the units for JC allergen as 10,000 JAU/mL, which was said to equal 12.5 μg/mL of Cry j 1.[14]

Outcomes

JC pollen and JCY pollen counts were recorded in central Tokyo by using the Durham method.[15] The peak JCY pollen dispersal period was defined as the 7 days including the first day of the first 2 consecutive days of 30 or more grains/cm^2 per day of JCY pollen dispersal. Because JCY pollen levels were extremely high in the fourth season (2018), the peak JCY dispersal period for 2018 was defined as April 1 to 8, a period consisting of (1) the days on which "more than 30 grains/cm^2 per day of JCY pollen were dispersed consecutively" and (2) "the day after the last day when 30 grains/cm^2 per day of JC pollen were dispersed" (the influence of JC pollen was considered to have decreased).

Nasal and eye symptom evaluation was based on the Japanese guidelines for allergic rhinitis[16] and on previous experience with the clinical development of JC pollen SLIT drops.[17] Efficacy was evaluated as TNSMSs, total ocular symptom and medication scores (TOSMSs), well days, severe symptom days, proportion of participants who did not use rescue medication, and cumulative frequency of rescue medication use during the peak JCY pollen dispersal periods from 2016 to 2019 (see Table E2). Use of rescue medication (ie, oral antihistamines, nasal vasoconstrictors, and eye drops) was permitted only when participants considered their symptoms to be intolerable; prophylactic administration was prohibited. The maximum score for the TNSMS was 18, based on a maximum score of 12 for symptoms and 6 for use of rescue medication (oral antihistamines and nasal vasoconstrictors). The maximum score for the TOSMS was 9, based on a maximum score of 6 for symptoms and 3 for use of rescue medication (eye drops). Details are available in the Supplementary Methods. Safety was evaluated by monitoring adverse events (AEs), including adverse drug reactions (ADRs), defined as study drug-related AEs starting at the initiation of the long-term treatment period. Serum JC pollen–specific IgE and JCY pollen–specific IgE levels were measured by using the ImmunoCAP assay (SRL and Torii, Tokyo, Japan).

Statistical analysis

The basis for the sample size of the 206-2-1 trial was described previously.[11] This *post hoc* analysis was not declared *a priori* in the original protocol. Efficacy data were analyzed for full analysis sets (FAS), which were defined separately for each season (Fig 1). Each FAS included all subjects who had reported symptom severity and medication use at least once during the peak JCY pollen dispersal period of the respective season. The evaluation period for efficacy assessments was the peak JCY pollen dispersal period. For the analysis, we used the linear model, generalized linear model, and logistic regression model with the treatment group as a fixed effect for efficacy evaluations. The main evaluation of this *post hoc* analysis was TNSMS during the peak JCY pollen dispersal period in the second season (2016). Paired comparisons were performed between the high-PP and high-PA subgroups as well as between the low-PP and low-PA subgroups based on the least squares (LS) mean. The Fieller theorem was used for calculating the CIs for the rate of decrease in the LS mean.[18] Details of the statistical analyses, including the secondary end points, are available in the Supplementary Methods. All statistical tests were performed using SAS software, version 9.3 or higher (SAS Institute, Cary, NC), with a 5% significance level. All tests and 95% CIs were 2 sided.

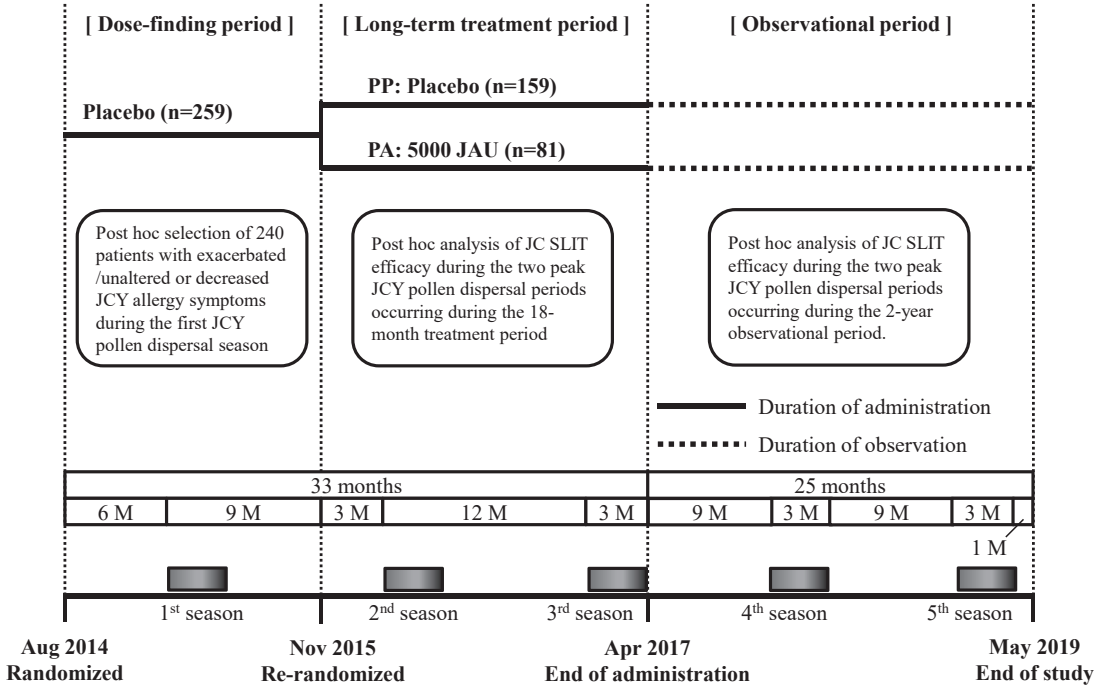

FIG 1. Trial design and *post hoc* analysis. Patients who received placebo during the dose-finding period and either placebo or 5000 JAU of JC pollen SLIT tablets were further segregated into subgroups based on exacerbation of rhinitis symptoms experienced during the first (2015) peak JCY pollen dispersal period. *Black boxes* show the overlapping JC and JCY pollen dispersal seasons.

RESULTS

Participants

At the end of the dose-finding period in the 206-2-1 trial, a total of 240 patients were rerandomized into the placebo (PP) group (n = 159) and the active drug (PA) group (n = 81). For the current *post hoc* analysis, we further assigned the patients into high-PP (n = 70), low-PP (n = 89), high-PA (n = 38), and low-PA (n = 43) groups based on exacerbation/no change (high) or a decrease (low) of rhinitis symptoms during the first (2015) peak JCY pollen dispersal period (see the Supplementary Methods and Fig E1 in the Online Repository at www.jaci-global.org). The baseline demographics and disease characteristics were not significantly different between the 4 groups (see Table E1 in the Online Repository at www.jaci-global.org). Of note, 72.9%, 81.6%, 80.9%, and 79.1% of patients in the high-PP, high-PA, low-PP, and low-PA groups, respectively, were sensitized to both JCY pollen (a specific IgE level of ≥0.70 UA/mL) and JC pollen (a specific IgE level of ≥3.5 UA/mL).

Pollen counts during the evaluation periods (peak JCY pollen dispersal periods)

Fig E2 (in the Online Repository at www.jaci-global.org) shows the cumulative pollen counts during the JC and JCY pollen dispersal seasons from 2015 to 2019. Table E2 shows the JCY pollen counts and dates for the complete JCY pollen dispersal seasons and the 7-day peak dispersal periods for each year (as defined in the Methods section). The cumulative JCY pollen counts during the peak JCY pollen dispersal periods were 604, 526, 897, 2685, and 959 grains/cm^2 in 2015, 2016, 2017, 2018, and 2019, respectively. Note that the peak JCY pollen dispersal period for 2018 was defined slightly differently from the other peak periods because of the abnormally high pollen levels during the 2018 JCY pollen dispersal season.

Exacerbation of rhinitis symptoms by JCY pollen

The average daily TNSMS for the FAS and the LS mean TNSMS are shown in Figs 2 and 3, respectively. A peak in average daily TNSMS was observed for all 4 patient groups at the start of the 2015 JC pollen dispersal season, but only the high-PP and high-PA groups exhibited a clear second peak in TNSMS during the JCY pollen dispersal season, which validates the patient subgroup selection method based on change in rhinitis symptoms. During the 2015 peak JCY pollen dispersal period, the LS mean TNSMSs were 8.17 and 7.68 for the high-PP and high-PA groups, respectively, and 5.76 and 5.80 for the low-PP and low-PA groups, respectively (Fig 3).

Efficacy

JC pollen SLIT tablets had a beneficial effect on JCY pollen allergy symptoms, as evidenced by the significant decreases in LS mean TNSMS (a decrease of ~30%-40%) between the PA groups and PP groups during the 2016-2019 peak JCY pollen dispersal periods (all $P < .01$ [Fig 3 and Table I]). Compared with the high-PP group, the high-PA group exhibited significant reductions in TNSMS of 33.0% (second season) and 39.1% (third season) during the treatment period and remained significantly reduced even in the fourth (35.2%) and fifth (33.6%) seasons after administration of JC pollen SLIT tablets had ceased. For the low-PA group, TNSMSs also decreased significantly

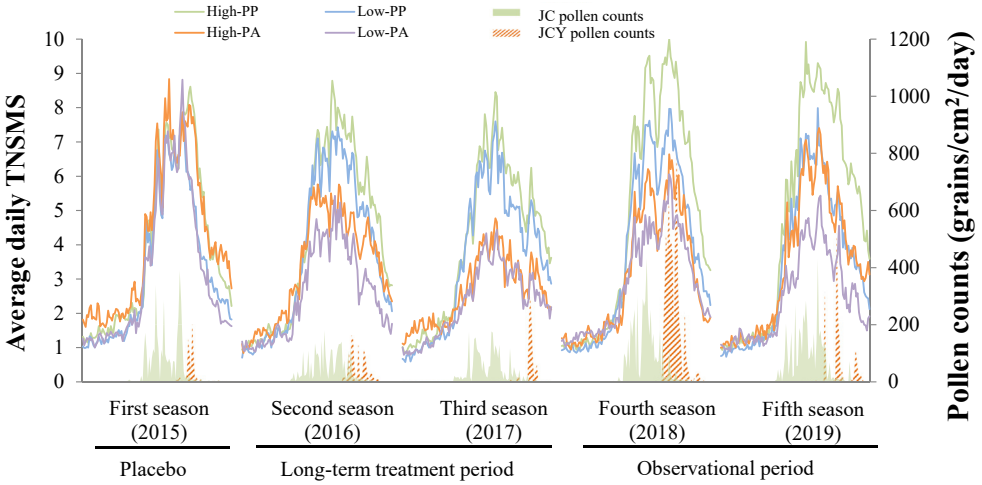

FIG 2. Average daily TNSMSs for the FAS (*solid lines*) and JC and JCY pollen counts (*green and orange shading, respectively*) during the 2015 to 2019 pollen dispersal seasons. High and low refer to patients who experienced an increase/no change or decrease, respectively, in symptoms during the peak JCY pollen dispersal period in 2015.

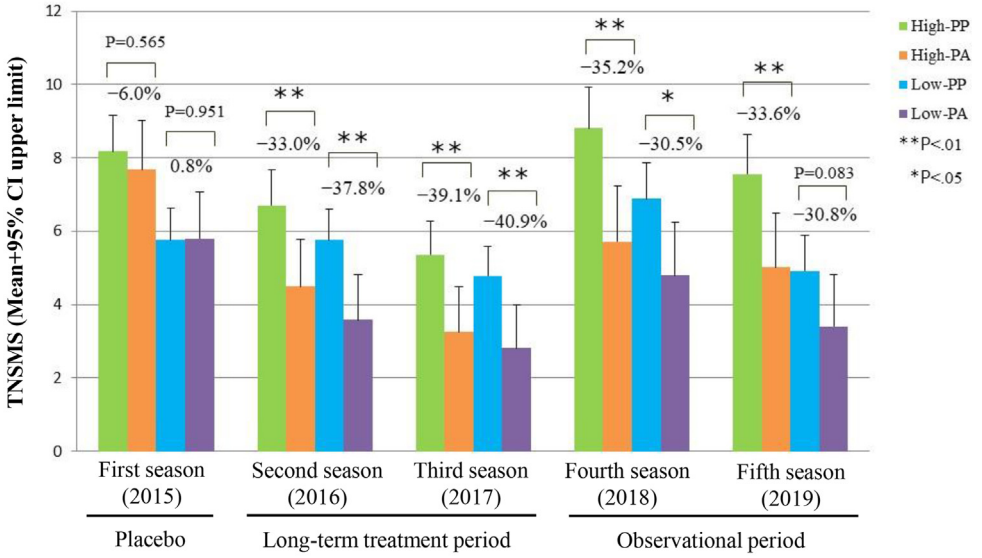

FIG 3. Effect of JC pollen SLIT therapy on TNSMS during the peak JCY pollen dispersal periods. Bars show the LS mean TNSMS with 95% CIs. Numbers show the relative difference (%) in TNSMS for each PA group versus for the corresponding PP group. High and low refer to patients who experienced an increase/no change or decrease, respectively, in symptoms during the peak JCY pollen dispersal period in 2015. $^{**}P < .01$ and $^{*}P < .05$ vs for the PP group.

compared with those for the low-PP group in the second season (37.8%) through the fourth season (30.5%) ($P < .05$), with the largest decrease occurring in the third season during the treatment period (40.9%).

The TOSMSs for the FAS during the 5 peak JCY pollen dispersal periods are shown in Table E3 (available in the Online Repository at www.jaci-global.org), and the average daily TOSMS and LS mean TOSMSs are shown in Figs E3 and E4 (see the Online Repository at www.jaci-global.org), respectively. TOSMS was significantly lower in the high-PA group than in the high-PP group in the second (36.4%) and fourth (38.9%) peak JCY pollen dispersal periods ($P < .05$), whereas significant decreases in the low-PA group compared with in the low-PP group were observed in the second (44.6%), third (56.3%), and fourth (35.9%) seasons ($P < .05$).

Table E4 (see the Online Repository at www.jaci-global.org) shows the individual component TNSMS scores (sneezing, runny nose, blocked nose, itchy eyes, watery eyes, oral antihistamine, nasal spray, ocular antihistamine) for all seasons. During the 2016-2019 peak JCY pollen dispersal periods, all LS mean scores

TABLE I. Analysis of rhinitis scores (TNSMSs) during the peak JCY pollen dispersal periods for the full analysis set

Treatment group	n	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI)	Relative difference vs PP group (95% CI)	*P* value
First season (2015) (linear model analysis*); dose-finding period (placebo)					
High-PP	70	8.17 (7.18-9.16)	—	—	—
High-PA	38	7.68 (6.34-9.02)	−0.49 (−2.16 to 1.18)	−6.0 (−24.7 to 15.5)	.565
Low-PP	88	5.76 (4.87-6.64)	—	—	—
Low-PA	43	5.80 (4.54-7.07)	0.05 (−1.49 to 1.59)	0.8 (−23.9 to 30.3)	.951
Second season (2016) (linear model analysis*); long-term treatment period					
High-PP	66	6.70 (5.73-7.67)	—	—	—
High-PA	38	4.49 (3.21-5.77)	−2.21 (−3.82 to −0.61)	−33.0 (−53.2 to −10.0)	**.007**
Low-PP	86	5.75 (4.90-6.60)	—	—	—
Low-PA	40	3.58 (2.33-4.82)	−2.18 (−3.69 to −0.67)	−37.8 (−60.2 to −12.8)	**.005**
Third season (2017) (linear model analysis*); long-term treatment period					
High-PP	64	5.35 (4.44-6.27)	—	—	—
High-PA	36	3.26 (2.04-4.48)	−2.09 (−3.62 to −0.57)	−39.1 (−62.7 to −11.9)	**.007**
Low-PP	81	4.78 (3.96-5.59)	—	—	—
Low-PA	39	2.82 (1.65-4.00)	−1.95 (−3.38 to −0.52)	−40.9 (−66.0 to −12.3)	**.008**
Fourth season (2018) (linear model analysis*); observational period					
High-PP	62	8.81 (7.68-9.94)	—	—	—
High-PA	34	5.71 (4.18-7.23)	−3.10 (−5.01 to −1.20)	−35.2 (−53.5 to −14.8)	**.002**
Low-PP	81	6.88 (5.89-7.87)	—	—	—
Low-PA	38	4.79 (3.34-6.23)	−2.10 (−3.85 to −0.34)	−30.5 (−52.4 to −5.6)	**.019**
Fifth season (2019) (linear model analysis*); observational period					
High-PP	61	7.56 (6.47-8.64)	—	—	—
High−PA	33	5.02 (3.53-6.50)	−2.54 (−4.38 to −0.70)	−33.6 (−54.2 to −10.2)	**.007**
Low-PP	77	4.92 (3.95-5.89)	—	—	—
Low-PA	36	3.40 (1.99-4.82)	−1.52 (−3.23 to 0.20)	−30.8 (−60.5 to 4.4)	.083

High and low refer to patients who experienced exacerbated/unaltered or decreased rhinitis symptoms, respectively, during the peak JCY pollen dispersal period in 2015 while receiving placebo. Bold type indicates a statistically significant value difference ($P < .05$).
*Dependent variable, each score; fixed effect, treatment groups.

were lower in the high-PA and low-PA groups than in the high-PP and low-PP groups, although not all of the differences were statistically significant.

Table E5 (in the Online Repository at www.jaci-global.org) shows the analysis of symptom relief during the 2015 to 2019 peak JCY pollen dispersal periods. The analysis included the proportion of patients with well days, severe symptom days, and no rescue medication use. Compared with the high-PP group, the high-PA group had more well days (54.2%, 60.7%, 30.8%, and 41.5% in the second through fifth seasons, respectively, vs 28.4%, 38.7%, 15.0%, and 31.1% in the high-PP group), fewer severe symptom days (17.9%, 10.3%, 24.6%, and 20.7%, respectively, vs 31.6%, 21.2%, 50.2%, and 36.2% in the high-PP group), and more patients who did not use rescue medications (76.3%, 86.1%, 64.7%, and 66.7%, respectively, vs 54.5%, 67.2%, 45.2%, and 54.1% in the high-PP group). Some of these differences were not statistically significant. Notably, similar results were obtained for the comparisons of the low-PA and low-PP groups.

Table E6 (see the Online Repository at www.jaci-global.org) shows the cumulative frequency of rescue medication use during each peak JCY pollen dispersal period. Rescue medication use was lower for the high-PA group than for the high-PP group and for the low-PA group than for the low-PP group in all 4 seasons evaluated.

Immunologic responses

Fig 4 shows the change from baseline in serum JC pollen–specific IgE and JCY pollen–specific IgE over the 5-year study period. The high-PP and low-PP groups showed small increases in the levels of JC and JCY pollen–specific IgE during the annual JC and JCY pollen dispersal period. In the fourth season (2018), the levels of JC and JCY pollen dispersal were higher than in previous years, and the increase in the peak of both IgE levels was high. However, in the high-PA and low-PA groups, levels of both JC and JCY pollen–specific IgE increased following the start of active treatment, and both IgE levels were unaffected by natural pollen exposure to JC and JCY pollen during the treatment period. There were no obvious differences in antipollen IgE levels between the high-PA and low-PA groups. There was a strong correlation between JC pollen–specific IgE and JCY pollen–specific IgE levels in the high-PA and low-PA groups during the first 4 months of JC pollen SLIT tablet administration ($r = 0.9237$ [Fig 5]).

Safety

Safety was analyzed starting at the end of the dose-finding period, when patients were rerandomized to the PP and PA groups. No AEs of anaphylaxis, serious ADRs, or ADRs requiring epinephrine were reported, and the overall incidence of AEs and ADRs during the 18-month treatment period was similar for the high-PA (73.7% and 18.4%, respectively) and low-PA (83.7% and 20.9%, respectively) groups (Table II). Most ADRs occurred during the first 2 weeks of JC pollen SLIT tablet administration in both the high-PA and low-PA groups, and the most common ADRs were mild local reactions at the site of administration (Tables III and IV). No new safety concerns emerged in the PA groups during the peak JCY pollen dispersal periods.

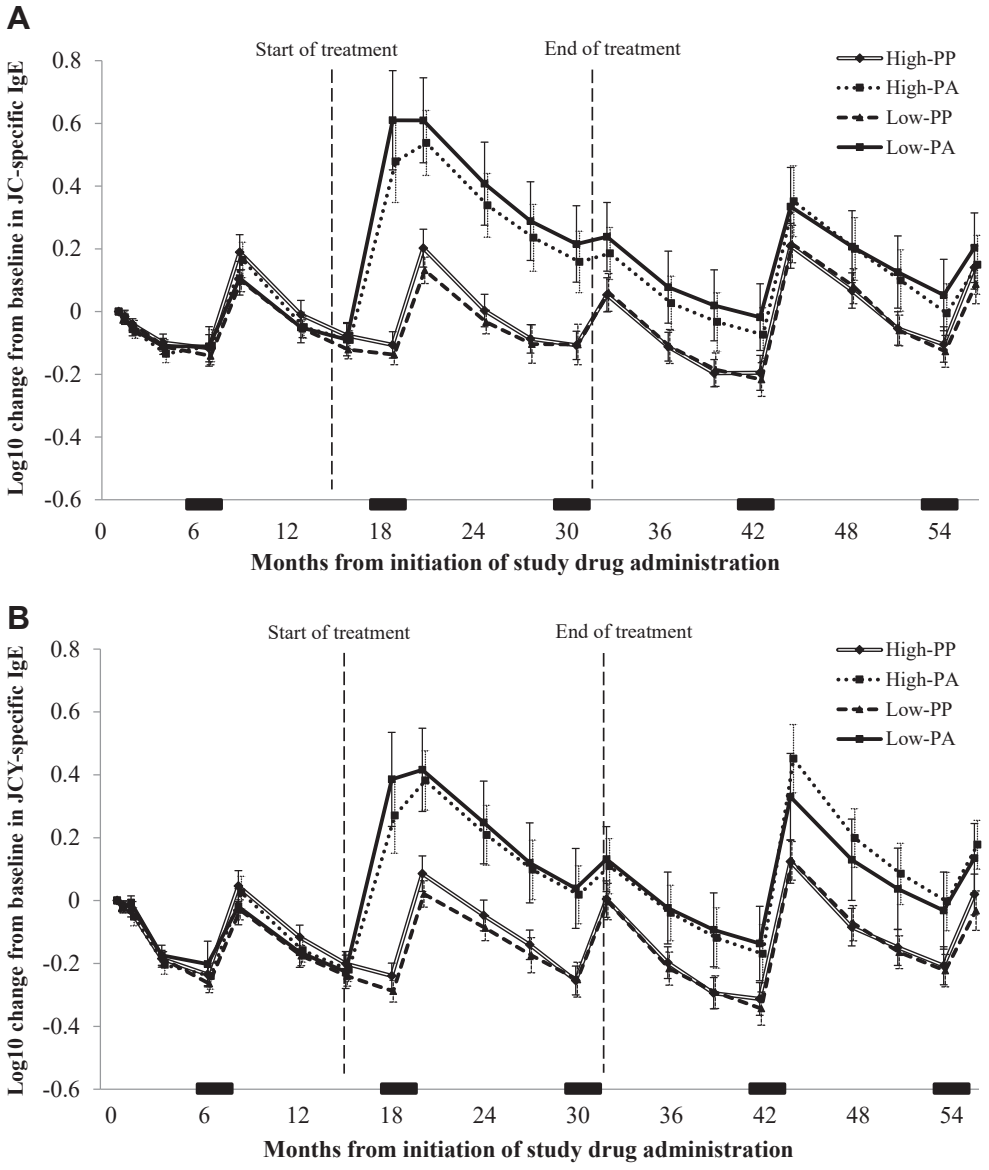

FIG 4. Change from baseline in levels of JC pollen–specific IgE (**A**) and JCY pollen–specific IgE (**B**) for the FAS. Data are presented as means ± 95% CIs. *Black boxes* show the overlapping JC and JCY pollen dispersal seasons. High and low refer to patients who experienced an increase/no change or decrease, respectively, in symptoms during the peak JCY pollen dispersal period in 2015.

DISCUSSION

Here, we have reported the first analysis of the efficacy of JC pollen SLIT tablets for the treatment of rhinitis symptoms caused by JCY pollen, a conifer related to JC. "Cypress pollinosis" is difficult to define in Japan because the JC pollen and JCY pollen dispersal seasons overlap, and almost all of the patients who test positive for JCY are also positive for JC pollen–specific IgE.[19] Clinical trial 206-2-1 evaluated the efficacy and safety of JC pollen SLIT tablets in patients with JC pollen allergy. At the time of enrollment, the participants' history of allergy caused by JC pollen was confirmed, but we did not confirm the presence or absence of symptoms caused by JCY pollen dispersal. Therefore, in the present *post hoc* analysis of 240 patients in the 206-2-1 trial, we sought to evaluate the impact of JC pollen SLIT tablets specifically on rhinitis symptoms caused by JCY pollen. We defined these patients on the basis of the change in TNSMS during the 7-day peak JCY pollen dispersal period in the first year of the study and included only those who received placebo during that period. The patient selection process for this *post hoc* analysis was verified by demonstrating that the high-PP and high-PA groups, but not the low groups, exhibited a peak in TNSMS that coincided with the peak JCY pollen dispersal period in 2015.

We found that treatment of the high-PA group with JC pollen SLIT tablets for 18 months significantly improved TNSMS not only throughout the 18-month treatment period but also throughout the 2-year observation period after treatment had ceased. Moreover, the magnitude of the symptom improvement (30%-40%) in the high-PA versus high-PP groups was essentially

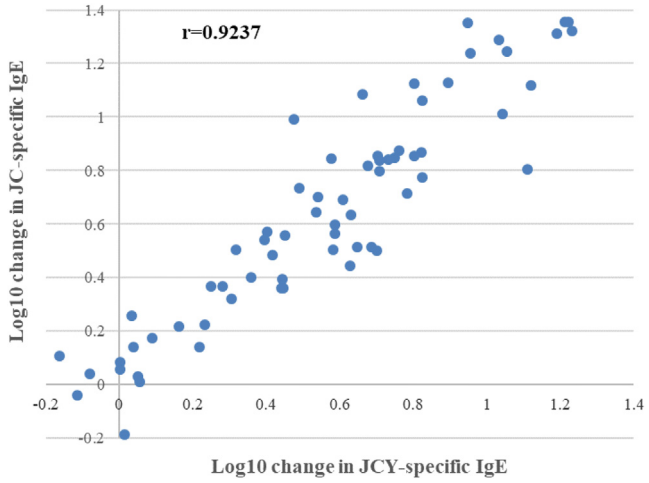

FIG 5. Correlation between the change in JC pollen–specific IgE and JCY pollen–specific IgE levels between baseline and 4 months of treatment with JC pollen SLIT tablets. *r* Value indicates Pearson correlation coefficient.

unchanged from the treatment period through the observation period, suggesting little to no waning of efficacy. These improvements exceeded the minimum clinically relevant effect required by the World Allergy Organization (>20% improvement vs placebo)[20] and US Food and Drug Administration (≥15% improvement vs placebo with a ≤10% upper limit for the 95% CI).[21-23] Recently, Boonpiyathad et al reported that house dust mite–specific allergen immunotherapy induced immunosuppressive innate lymphoid cells during the treatment, which might be associated with the improvement observed after treatment[24] Studies of the effects of SLIT tablets on pollens within the homologous group have also been published. Ellis et al found that the administration of timothy grass SLIT tablets had no effect on symptoms caused by nonhomologous birch pollen[25] and Couroux et al found that the administration of standardized quality (SQ) tree SLIT tablets reduced allergic rhinosinusitis symptoms caused by homologous birch or oak pollen.[26] In the present study, innate immunity might have contributed to the effect of JC pollen SLIT tablets on allergic symptoms caused by JCY pollen; however, the "clinically meaningful difference" observed when the treatment group was compared with the placebo group persisted for 2 years and continued for 2 years after the end of treatment might be largely related to the cross-reactivity of JC pollen SLIT tablets among homologous pollen groups. Furthermore, the numbers of well days, severe symptom days, and proportion of participants who did not use rescue medications, which are generally considered to be the most meaningful clinical outcomes to the patient, were clearly improved in the high-PA group versus in the high-PP group. Treatment efficacy during the peak JCY pollen dispersal period resulted in a simultaneous improvement in symptoms and a reduced need for symptom-relieving medications. In the 206-2-1 trial, use of rescue medication was permitted only when participants found their symptoms intolerable. In this *post hoc* analysis, the reduction of use of medications for symptom relief, even during the short period of the peak JCY pollen dispersal period, is particularly important because it shows that the benefits provided by JC pollen SLIT tablets also benefited allergic symptoms caused by homologous pollen. These results indicate that JC pollen SLIT tablets provide real-world clinical benefit in alleviating the symptoms of JCY pollen allergy and improving the quality of life of patients with allergy. Interestingly, although those in the low-PA group were patients who received placebo and exhibited no quantifiable increase in rhinitis symptoms during the peak JCY pollen dispersal period in the first year, they too experienced a range of beneficial effects similar to those experienced by the low-PP group, as did those in the high-PA group. Even in the "low" group, the patients were clinically and immunologically affected by annual cypress pollen dispersal, suggesting that administration of JC pollen SLIT tablets was effective.

We previously reported that patients treated with JC pollen SLIT tablets had increased serum levels of JC pollen–specific IgE and JC pollen–specific IgG4, suggesting that SLIT induces immunomodulation and/or subsequent clinical tolerance.[13] In the present study, the placebo group showed similar increased peaks in their levels of JC pollen–specific (log_{10} change in the second season = 0.27-0.31) and JCY pollen–specific (log_{10} change in the second season =0.31-0.32) IgE related to annual natural pollen exposure, and there was no difference in the degree of increase in levels of JC pollen– and JCY pollen–specific IgE, even in the fourth season (JC pollen–specific IgE level = 0.41-0.43 and JCY pollen–specific IgE level = 0.44-0.47), when the amount of JCY pollen dispersal was much higher (2685 grains/cm^2in the fourth season vs 526-959 grains/cm^2in the other seasons). In contrast, the increases in JC pollen– and JCY pollen–specific IgE levels observed in the active drug groups, low-PA and high-PA, began to increase "after switching from placebo to JC pollen SLIT tablets" before the JC pollen began to disperse. About 4 months after JC pollen SLIT tablet initiation, the changes were similar: the JC pollen–specific IgE level ranged from 0.57 to 0.71, and the JCY pollen–specific IgE level ranged from 0.49 to 0.62. Compared with the placebo group, this was an increase from before the JC pollen had begun to disperse, which was different from the pattern of increase and amount of change observed in the placebo group during the "period of JC and JCY pollen dispersal" (JC pollen–specific IgE level = 0.27-0.31 and JCY pollen–specific IgE level = 0.31-0.32 for the dispersal period). These were the elevated JC pollen–specific IgE and JCY pollen–specific IgE levels resulting from the administration of JC pollen SLIT tablets rather than from stimulation by seasonal pollen dispersal. Regarding the Cupressaceae group allergens, *in vitro* inhibition and absorption tests using sera positive for JCY pollen indicated the specific IgE cross-reactivity between JC and JCY pollens.[19] Taken together, (1) the high natural exposure to JCY pollen in the fourth season and (2) the administration of JC pollen SLIT tablets resulted in similar responses of JC pollen– and JCY pollen–specific IgE levels, suggesting that JC and JCY pollen can each induce a highly cross-reactive immune response against other pollens in the homologous Cupressaceae group. JCY pollen–specific IgG4 levels were not analyzed in the current study because a validated assay system for specific IgG4 has yet not been established.

The efficacy of SLIT tablets targeting allergens from birch-homologous trees, such as alder, hornbeam, hazel, and oak, have been studied in a phase III study of SQ tree SLIT tablets, which contained standardized birch pollen allergens. The results of that study showed that changes in birch (*Betula verrucosa*)-specific IgE and birch-specific IgG4 levels correlated with changes in IgE and IgG4 specific for alder (*Alnus glutinosa*), hazel (*Corylus avellana*), and oak (*Quercus alba*)

TABLE II. Evaluation of safety in the rerandomized PP and PA groups

Period	High-PP (n = 70)		High-PA (n = 38)		Low-PP (n = 89)		Low-PA (n = 43)	
Dose-finding period (2015, placebo)								
Serious AE, no. (%)	1	1.4	—	—	2	2.2	2	4.7
Serious ADR, no. (%)	—	—	—	—	—	—	—	—
All AEs, no. (%)	56	80.0	28	73.7	62	69.7	37	86.0
Mild	55	78.6	24	63.2	59	66.3	32	74.4
Moderate	—	—	4	10.5	3	3.4	5	11.6
Severe	1	1.4	—	—	—	—	—	—
All ADRs, no. (%)	13	18.6	4	10.5	17	19.1	9	20.9
Mild	13	18.6	4	10.5	17	19.1	9	20.9
Moderate	—	—	—	—	—	—	—	—
Severe	—	—	—	—	—	—	—	—
Long-term treatment period (2016–2017)								
Serious AE, no. (%)	—	—	—	—	3	3.4	—	—
Serious ADR, no. (%)	—	—	—	—	—	—	—	—
All AEs, no. (%)	55	78.6	28	73.7	64	71.9	36	83.7
Mild	53	75.7	27	71.1	56	62.9	34	79.1
Moderate	2	2.9	1	2.6	8	9.0	2	4.7
Severe	—	—	—	—	—	—	—	—
All ADRs, no. (%)	2	2.9	7	18.4	5	5.6	9	20.9
Mild	2	2.9	7	18.4	5	5.6	9	20.9
Moderate	—	—	—	—	—	—	—	—
Severe	—	—	—	—	—	—	—	—
	High-PP (n = 64)		**High-PA (n = 36)**		**Low-PP (n = 81)**		**Low-PA (n = 39)**	
Observation period (2018–2019)								
Serious AE, no. (%)	2	3.1	2	5.6	2	2.5	1	2.6
Serious ADR, no. (%)	—	—	—	—	—	—	—	—
All AEs, no. (%)	47	73.4	26	72.2	58	71.6	29	74.4
Mild	42	65.6	25	69.4	52	64.2	27	69.2
Moderate	5	7.8	1	2.8	6	7.4	2	5.1
Severe	—	—	—	—	—	—	—	—
All ADRs, no. (%)	—	—	—	—	—	—	—	—
Mild	—	—	—	—	—	—	—	—
Moderate	—	—	—	—	—	—	—	—
Severe	—	—	—	—	—	—	—	—

High and low refer to patients who experienced exacerbated/unaltered or decreased rhinitis symptoms, respectively, during the peak JCY pollen dispersal period in 2015 while taking placebo.

allergens in patients administered SQ tree pollen SLIT tablets.[27,28] Although we could not measure JCY pollen–specific IgG4 in the present study, the results of JC pollen- and JCY pollen–specific IgE analysis substantiate the notion that SLIT with 1 allergen can elicit cross-reactive immunity to related allergens. This finding has important ramifications for the possible treatment of other allergens from homologous species.

In terms of the safety of JC pollen SLIT tablets for the treatment of JCY pollen allergy, our analysis revealed no AEs of anaphylaxis and no serious AEs or ADRs, consistent with our previous reports. A mild local reaction at the site of administration was limited to the early days of the treatment period. No new or exacerbated ADRs were detected during the peak JCY pollen dispersal periods during either the treatment or follow-up periods.

Our study has some limitations, the main one being that this was a *post hoc* analysis, not a prospective evaluation. In Japan, it has been reported that no patients were sensitized only to JCY pollen.[19] In addition, it is difficult to characterize allergic rhinitis caused solely by JCY pollen because of the overlap in the dispersal period of JC pollen and JCY pollen, and these factors make direct evaluation difficult. Further immunologic studies including JCY pollen–specific IgG4- or IgE-blocking factor in addition to JCY pollen–specific IgE would be necessary for further consideration. Future studies will investigate the reproducibility of the efficacy of JC pollen SLIT tablets for JCY pollen rhinitis symptoms.

In conclusion, this *post hoc* analysis of data from the 206-2-1 clinical study of JC pollen SLIT tablets provides support for their efficacy against rhinitis symptoms caused by JCY pollen. Both the persistence of the beneficial effects after discontinuation of treatment and the analysis of pollen-specific IgE levels suggest that JC pollen SLIT tablets induce cross-reactive immunity to JCY pollen. Although these findings have implications for the treatment of patients with rhinitis symptoms caused by JCY pollen, SLIT agents are not currently approved for the treatment of JCY pollen allergy in Japan. The use of JC pollen SLIT tablets to treat patients with JC and/or JCY pollen allergies simplifies treatment with the separate allergen immunotherapies and further suggests a new treatment strategy for allergic diseases.

TABLE III. Common ADRs (experienced by 2 or more patients) during the dose-finding period (2015, placebo)

	High-PP (n = 70)		High-PA (n = 38)		Low-PP (n = 89)		Low-PA (n = 43))	
ADR	No.	%	No.	%	No.	%	No.	%
Rhinorrhea	4	5.7	2	5.3	6	6.7	2	4.7
Eye pruritus	1	1.4	1	2.6	2	2.2	3	7.0
Stomatitis	—	—	1	2.6	1	1.1	2	4.7
Sneezing	1	1.4	2	5.3	1	1.1	1	2.3
Throat irritation	1	1.4	1	2.6	2	2.2	1	2.3
Laryngeal discomfort	1	1.4	1	2.6	—	—	1	2.3
Pruritus	—	—	1	2.6	1	1.1	—	—
Nasal congestion	5	7.1	1	2.6	4	4.5	—	—
Nasal discomfort	1	1.4	1	2.6	3	3.4	—	—
Ear pruritus	2	2.9	1	2.6	1	1.1	—	—
Oropharyngeal discomfort	1	1.4	—	—	1	1.1	1	2.3
Diarrhea	—	—	—	—	1	1.1	1	2.3
Headache	—	—	—	—	1	1.1	1	2.3
Palpitations	1	1.4	—	—	—	—	1	2.3
Rash	1	1.4	—	—	1	1.1	—	—
Rhinitis	1	1.4	—	—	1	1.1	—	—

High and low refer to patients who experienced exacerbated/unaltered or decreased rhinitis symptoms, respectively, during the peak JCY pollen dispersal period in 2015 while taking placebo.

TABLE IV. Common ADRs (experienced by 2 or more patients) during the long-term treatment period (2016-2017)

	High-PP (n = 70)		High-PA (n = 38)		Low-PP (n = 89)		Low-PA (n = 43)	
ADR	No.	%	No.	%	No.	%	No.	%
Oral pruritus	—	—	3	7.9	—	—	3	7.0
Oedema mouth	—	—	3	7.9	—	—	3	7.0
Throat irritation	—	—	1	2.6	1	1.1	2	4.7
Oral mucosal erythema	—	—	1	2.6	—	—	1	2.3
Oral discomfort	—	—	1	2.6	—	—	1	2.3
Nasal discomfort	1	1.4	—	—	1	1.1	1	2.3
Pruritus	1	1.4	—	—	1	1.1	—	—

High and low refer to patients who experienced exacerbated/unaltered or decreased rhinitis symptoms, respectively, during the peak JCY pollen dispersal period in 2015 while taking placebo.

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Clinical implications: JC pollen SLIT tablets may be effective for the treatment of patients with JC-JCY pollinosis, thereby simplifying immunotherapy and suggesting a new approach to treating diseases caused by homologous allergens.

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