



Contents lists available at ScienceDirect

Allergy International

journal homepage: <http://www.elsevier.com/locate/alit>

Original Article

Long-term treatment of Japanese cedar pollinosis with Japanese cedar pollen SLIT drops and persistence of treatment effect: A post-marketing clinical trial

Yasuyuki Nomura ^{a, b}, Kimihiro Okubo ^c, Tadashi Nakamura ^d, Seiji Sawaki ^e,
Hideto Kitagou ^f, Norio Idei ^g, Shinya Kaneko ^{h, *}, Satoko Kobayashi ^h, Yusuke Tanaka ^h,
Yoshitaka Okamoto ^{i, j}

^a Department of Otolaryngology-Head and Neck Surgery, Nihon University School of Medicine, Tokyo, Japan^b Koganeibashi Sakura Clinic, Tokyo, Japan^c Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan^d Nakamura ENT Clinic, Kanagawa, Japan^e Kikuna Otolaryngology Clinic, Kanagawa, Japan^f Kitagou Otorhinolaryngology Clinic, Kanagawa, Japan^g IDEI ENT Clinic, Kanagawa, Japan^h Torii Pharmaceutical Co., Ltd, Tokyo, Japanⁱ Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan^j Chiba Rousai Hospital, Chiba, Japan

ARTICLE INFO

Article history:

Received 26 November 2019

Received in revised form

10 May 2020

Accepted 15 May 2020

Available online xxx

Keywords:

Allergic rhinitis

Effect persistence

Japanese cedar pollen

Long-term treatment

Sublingual immunotherapy

Abbreviations:

ADR, Adverse drug reaction; AE, Adverse event; FAS, Full analysis set; JAU, Japanese allergy unit; JC, Japanese cedar; SLIT, Sublingual immunotherapy; TNSS, Total nasal symptom score; TOSS, Total ocular symptom score; TNOSS, Total nasal and ocular symptom score; TNOMS, Total nasal and ocular medication score; TNSMS, Total nasal symptom and medication score; TOSMS, Total ocular symptom and medication score; TNOSMS, Total nasal and ocular symptom and medication score; WHO, World Health Organization

ABSTRACT

Background: There have been no reports of treatment effect persistence after long-term sublingual immunotherapy (SLIT) in patients with Japanese cedar (JC) pollinosis. Therefore, we conducted a post-marketing clinical trial to investigate the efficacy, safety, and effect persistence of JC pollen SLIT drops after approximately 3 years of treatment.

Methods: This was an open-label trial of 233 patients with JC pollinosis who were treated with JC pollen SLIT drops for approximately 3 years (2015–2017) and followed-up for an additional 2 years (2018–2019). Efficacy and effect persistence were evaluated using nasal and ocular symptom scores, daily use of rescue medication, and Japanese Rhinoconjunctivitis Quality of Life Questionnaire scores recorded during the JC pollen dispersal season of each year. Safety was evaluated by monitoring adverse events and adverse drug reactions.

Results: The mean combined total nasal symptom and medication score (range 0–18) during the peak symptom periods of 2015 through 2019 were 5.47 ± 3.38 , 4.52 ± 3.13 , 3.58 ± 2.63 , 5.28 ± 4.01 , and 6.83 ± 4.65 , respectively. The percentage of patients who used no rescue medications during the same periods was 64.8%, 75.2%, 80.3%, 63.7%, and 50.3%, respectively. A total of 138 adverse drug reaction incidents were recorded in 73 of the 233 patients (31.3%), of which 134 incidents (97.1%) were mild in severity.

Conclusions: JC pollen SLIT drops demonstrated treatment duration-dependent efficacy with effects that persisted for 2 years after cessation of treatment. The drug had a favorable safety profile over the 5-year study period.

Copyright © 2020, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author. Department of Clinical Development, Torii Pharmaceutical Co., Ltd, 3-4-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8439, Japan.

E-mail address: shinya.kaneko@torii.co.jp (S. Kaneko).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2020.05.008>

1323-8930/Copyright © 2020, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The most common form of seasonal allergic rhinitis in Japan is Japanese cedar (JC) pollinosis,^{1–4} caused by JC pollen. The Japanese guidelines for the management of allergic rhinitis indicate a prevalence of JC pollinosis of 26.5%.⁵ More recent immunological surveys report prevalences of 36.7% and 45.6%,^{6,7} suggesting that the number of affected individuals continues to rise.

Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the two main types of allergen-specific immunotherapy. SCIT has been administered in Japan since the 1960s, but it has several limitations, such as painful injections, the need for periodic hospital visits in the long term, and the potential for severe adverse drug reactions (ADRs). In an effort to address these problems, research into SLIT as an alternative treatment for JC pollinosis began in Japan in the early 2000s,^{8–10} and successful clinical trials¹¹ led to the eventual approval of JC pollen SLIT drops (CEDARTOLEN®) in October 2014. Over the past 5 years, SLIT for JC pollinosis has grown in popularity, and the efficacy and safety of long-term treatment with JC pollen SLIT drops have been established in the clinical setting.¹²

The strengths of allergen-specific immunotherapy include the persistence of treatment effects,^{13,14} the ability to suppress sensitization to new allergens,¹⁵ and the ability to control the onset of asthma in young patients with allergic rhinitis.¹⁶ While the effect persistence of short-term (15 months) SLIT tablets for JC pollinosis has been reported,^{17,18} there have been no studies of effect persistence following treatment for 3 or more years, which is the period recommended by both the Japanese and European guidelines.^{5,19} In the present study, we report the results of a post-marketing clinical trial of patients who were administered JC pollen SLIT drops for approximately 3 years (up to 33 months) and monitored for an additional 2 years following treatment cessation.

Methods

Trial design and intervention medication

This was a multicenter, open-label trial with a treatment period of approximately 33 months followed by a 2-year observation period. Participants were enrolled at five facilities in and around Tokyo between August and September 2014. The participants received JC pollen SLIT drops (CEDARTOLEN, manufactured and provided by Torii Pharmaceutical, Tokyo, Japan) sublingually once daily. Participants were instructed to hold the drops under their tongue for 2 min before being swallowed and not rinse their mouths, eat, or drink for an additional 5 min. The dose was gradually increased from 40 Japanese allergy units (JAU) to 2000 JAU during the first 2 weeks of treatment and maintained at 2000 JAU thereafter. The first dose was administered at a medical facility and patients were observed by a doctor for 30 min after dosing.

This trial (JapicCTI-142585) complied with the tenets of the Declaration of Helsinki and the study design was approved by examination committees of each participating medical institution. Written consent was obtained from all participants (or legal representatives for those ≤ 19 years of age) before they entered the study.

Participants

The inclusion criteria were: male or female participants living, working, or attending school in the south Kanto region; age 12–64 years; serum JC pollen-specific IgE level ≥ 3.5 UA/mL; and moderate-to-severe nasal allergy symptoms, as defined by the Japanese guidelines for allergic rhinitis,⁵ for at least 1 week during

the JC pollen dispersal seasons in each of the preceding 2 years. The exclusion criteria were: participants with perennial allergic rhinitis, medication-related allergic rhinitis, vasomotor rhinitis, or non-allergic rhinitis requiring treatment; diagnosis of oral allergy syndrome; concomitant food allergies; specific IgE level of ≥ 50 UA/mL against *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat dander, dog dander, Japanese cypress, orchard grass, or alder allergens; laser treatment or surgery for nasal symptoms within the preceding 3 years; previous allergen-specific immunotherapy for JC pollinosis; asthma attack in the preceding 5 years; history of hypersensitivity to the rescue medications used in this study (see below); history of anaphylaxis or angioedema; or pregnant.

Endpoint measures

Participants self-evaluated three nasal symptoms (sneezing, runny nose, and blocked nose), each on a 5-point scale of 0–4 (maximum 12) and two ocular symptoms (itchy eyes and watery eyes), each on a 4-point scale of 0–3 (maximum 6) by recording them in a daily electronic diary between January 8 and April 30 of each year. This method of symptom scoring has previously been used in clinical trials of JC pollinosis^{11,17,18} (Supplementary Tables 1–3).

During the same period, participants were forbidden to use antihistamines, systemic steroids, steroid nasal sprays, or other drugs intended to treat JC pollinosis. The participants were provided with acceptable rescue medications (antihistamine tablets, eye drops, and nasal vasoconstrictors) to treat symptoms of rhinitis or conjunctivitis deemed unbearable (a score of 4 for a nasal symptom or 3 for an ocular symptom, in addition to the explicit use of the word “unbearable” to describe the symptom). To standardize rescue medication use, unbearable “blocked nose” symptoms were treated with tramazoline hydrochloride nasal drops, and unbearable ocular symptoms were treated with ketotifen fumarate eye drops. If the drugs did not alleviate the symptoms, patients were treated with fexofenadine hydrochloride tablets. “Unbearable sneezing” or “runny nose” symptoms were also treated with fexofenadine hydrochloride tablets. Patients also recorded rescue medication daily using the electronic diary between the same period of January 8 and April 30 of each year. Rescue medication use was scored on a binary scale of 0 or 3 for days without or with medication use, respectively. Preventative use of rescue medications was forbidden, as was the use of masks, goggles, or other equipment to provide physically shielding from pollen.

The primary endpoint was total nasal symptom and medication score (TNSMS, range 0–18) during the peak symptom period of the JC pollen dispersal season each year (Supplementary Table 3), as has been used in previous clinical trials of JC pollinosis.^{11,17,18} Secondary endpoints were various individual and combinations of symptom and medication scores: individual symptom score, individual medication score, total nasal symptom score (TNSS), total ocular symptom score (TOSS), total nasal and ocular symptom score (TNOSS), total nasal and ocular medication score (TNOMS), TNSMS, total ocular symptom and medication score (TOSMS), and total nasal and ocular symptom and medication score (TNOSMS) (Supplementary Table 3). The number of patients who did not use rescue medications was also recorded. “Well days” were defined as days in which all nasal and ocular symptom scores were ≤ 1 and rescue medications were not used. “Severe symptom days” were defined as days in which at least one nasal or ocular symptom score was the maximum (4 for a nasal symptom score or 3 for an ocular symptom score). The Japanese Rhinoconjunctivitis Quality of Life Questionnaire was administered twice yearly on March 15 and March 31.

Scores were evaluated over two periods per year: the peak symptom period and the JC pollen dispersal season. The peak

symptom period for each patient was defined as the 3-week period that included the week with the highest TNSMS, plus the week preceding and following it. However, the dispersal season for Japanese cypress pollen generally starts at the beginning of April; therefore, to prevent allergic symptoms caused by Japanese cypress pollen being a confounding factor, we set March 31 as the final day of the peak symptom period. The start of the JC pollen dispersal season was defined as the first of the first two consecutive days after January 1 of a given year on which 1 pollen grain/cm² was detected. The end of the JC pollen dispersal season was defined as the day before the first of three consecutive days on which 0 pollen grain/cm² was detected.

Immunological testing for JC pollen-specific serum IgE and IgG4 was performed by SRL Corporation (Tokyo, Japan). Safety was evaluated by recording adverse events (AEs) occurring after initiation of treatment with JC pollen SLIT drops.

Statistical analysis

The number of patients in this trial was 230, which was the same size as the JC pollen SLIT tablet group in a concurrent phase II/III clinical trial occurring at the same time.^{17,18} Of the 230 enrolled patients, 200 were including in the full analysis set (FAS) at the end of the first season, which was sufficient to enable a longitudinal evaluation through the fifth year of the trial. Continuous data extracted from patient diaries are presented as the mean, standard deviation (SD), and 95% confidence intervals (CIs) as indicated. Binary data are presented as percentages and 95% CIs. The comprehensive status of the Japanese Rhinoconjunctivitis Quality of Life Questionnaire was evaluated using frequency totals, and regional scores are presented as the mean and SD.

Results

Participants

A total of 233 patients were enrolled at five medical institutions in and around the Tokyo area and received at least one dose of intervention medication between August 2014 and May 2019. More

than 50% of the participants were aged 30–49 years, and fewer than 10% were aged ≤19 years (Table 1). In total, 16.3% of the subjects were monosensitized to JC pollen, and 72.5% were sensitized to both JC pollen and cypress pollen (Table 1). Of the 233 patients, 190 completed the 33-month medication phase. The number of patients in the FAS at the end of the first through fifth seasons (2015–2019) was 219, 206, 193, 182, and 171, respectively (Fig. 1).

JC pollen counts

JC pollen counts were determined using the Durham method, and the data were obtained from the Tokyo Health and Safety

Table 1
Baseline characteristics.

	JC pollen SLIT drops N = 233
Male	107 (45.9%)
Monosensitized	38 (16.3%)
Cypress pollen-sensitized [†]	169 (72.5%)
Age (y), no. (%)	
12 to 19	20 (8.6%)
20 to 29	52 (22.3%)
30 to 39	54 (23.2%)
40 to 49	82 (35.2%)
50 to 64	25 (10.7%)
Mean ± SD	36.5 ± 11.6
Years with JC pollinosis, no. (%)	
<5	12 (5.2%)
≥5 to <10	36 (15.5%)
≥10 to <15	59 (25.3%)
≥15 to <20	50 (21.5%)
≥20	76 (32.6%)
Mean ± SD	16.3 ± 8.3
JC pollen-specific IgE (UA/mL), no. (%)	
≥3.5 to <17.5	120 (51.5%)
≥17.5 to <50	73 (31.3%)
≥50 to <100	32 (13.7%)
≥100	8 (3.4%)

[†] Cypress pollen sensitization was defined as a cypress pollen-specific IgE level of ≥0.70 UA/mL. JC, Japanese cedar; SD, standard deviation.

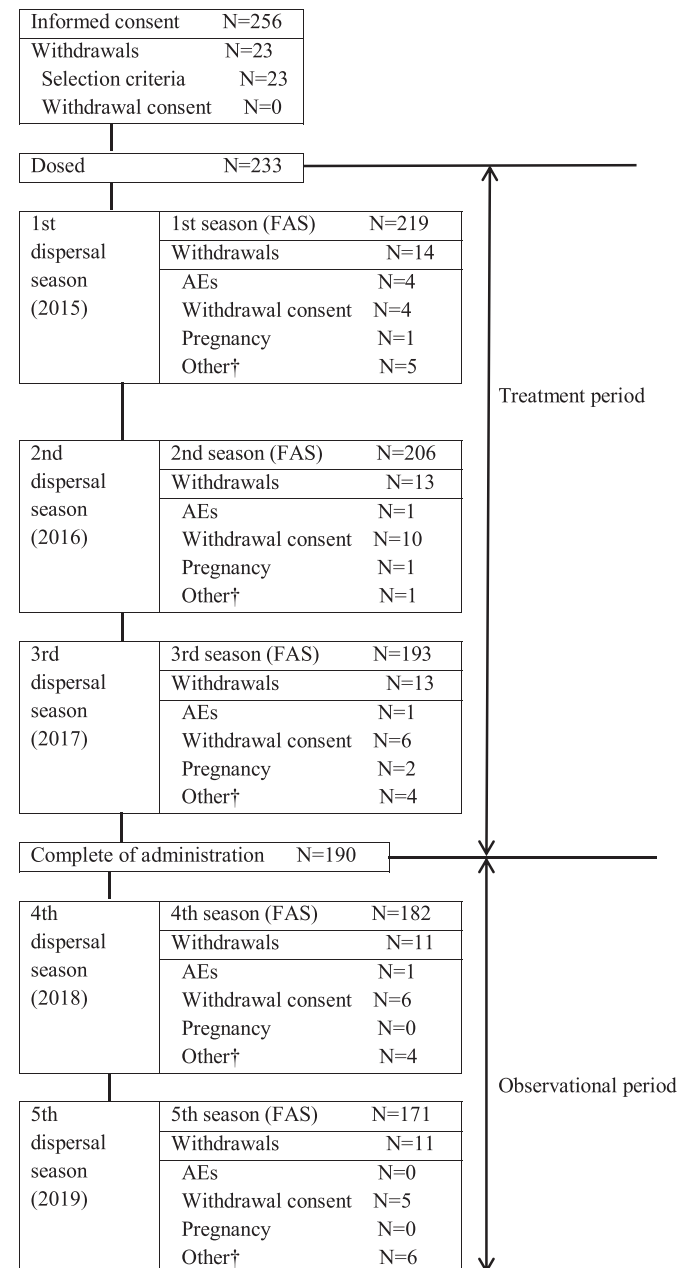


Fig. 1. Participant disposition. The full analysis set (FAS) for each year included participants who recorded at least one symptom score and medication score during the peak symptom period. † Other reasons for withdrawal included “lost to follow-up,” “moved from the trial area,” or “other.”

Center. The JC pollen counts during the peak symptom periods of the first through fifth seasons were 1472.5, 1569.0, 1359.1, 3343.2, and 2096.0/cm², respectively. The total JC pollen counts during each of the full dispersal seasons (up to April 30) were 3892.4, 2994.0, 2894.1, 5015.9, and 4960.1/cm², respectively (Supplementary Table 4). In 2018, the highest amount of Japanese cypress pollen dispersal on the past was observed, and approximately half of this pollen dispersal occurred in March. The peak symptom period was previously defined in trial protocols as a period (up to March 31) in which JC pollen would be a causative factor of the observed symptoms. However, in 2018, a period in which Japanese cypress pollen may have been a factor was considered as the peak symptom period. After considering the effects of this phenomenon on our evaluation of the intervention medication, we decided to truncate our calculation of the peak symptom period of 2018 to March 26, 2018. After this date, a clear effect of Japanese cypress pollen on the patients' symptoms could be observed (Fig. 2D).

Efficacy

The mean TNSMS during the peak symptom period, the primary endpoint, for the first through fifth seasons were 5.47 ± 3.38 , 4.52 ± 3.13 , 3.58 ± 2.63 , 5.28 ± 4.01 , and 6.83 ± 4.65 , respectively. Although JC pollen counts during the peak symptom periods in 2018 and 2019 (the 2 follow-up years) were higher than in the preceding 3 years, the TNSMS in the fourth season was similar to that in the first season. The highest TNSMS was recorded in the fifth season, 2 years after treatment cessation (Fig. 2A–E, Table 2).

Analysis of the clinically significant endpoints indicated that the percentage of participants who used no rescue medications during the five peak symptom periods ranged from 50.3% to 80.3%, while the percentage of “well days” and “severe symptom days” over the same times was 29.38%–56.78% and 8.87%–33.53%, respectively.

Treatment effects were observed for each of these endpoints. The percentage of participants with mean TNSMS <3 during the peak symptom period²⁰ ranged from 47.7% in the third season to 18.7% in the fifth season, suggesting effect persistence (Table 3). The scores for the JRQLQ administered on March 15 and March 31 of each season were compared separately. The scores were broadly similar in the first through the third seasons, with the best scores observed during the third season on both dates. With regard to the March 15 dataset, the scores in the fourth season were comparable to those in the first season, while the scores were worst in the fifth season. In contrast, the March 31 dataset showed that the scores in the fourth season were comparable to or worse than those in the fifth season, which, in turn, were worse than the scores in the first season (Table 4). The secondary endpoints (TNSS, TOSS, TNOSS, TNOMS, TOSMS, and TNOSMS) exhibited trends similar to that of TNSMS, with treatment effects persisting into the fourth and fifth seasons (Table 2).

Safety

No severe ADRs, AEs requiring the use of epinephrine, or anaphylaxis (as determined by the trial investigator or in accordance with the World Allergy Organization systemic allergic reaction grading system²¹) were observed in this trial. A total of 1537 AEs were recorded in 203 patients (87.1%), and 138 ADRs were recorded in 73 patients (31.3%) (Table 5). The incidence of AEs and ADRs was not significantly affected by age, duration of JC pollinosis history, or JC pollen-specific IgE levels (Supplementary Table 5). The most commonly observed ADRs were oral paresthesia, throat irritation, and oral edema; these have also been observed in other SLIT studies. Four participants (1.7%) withdrew from the study due to ADRs. None of the ADRs were considered severe, and the four considered moderate occurred in two patients (0.9%): one patient

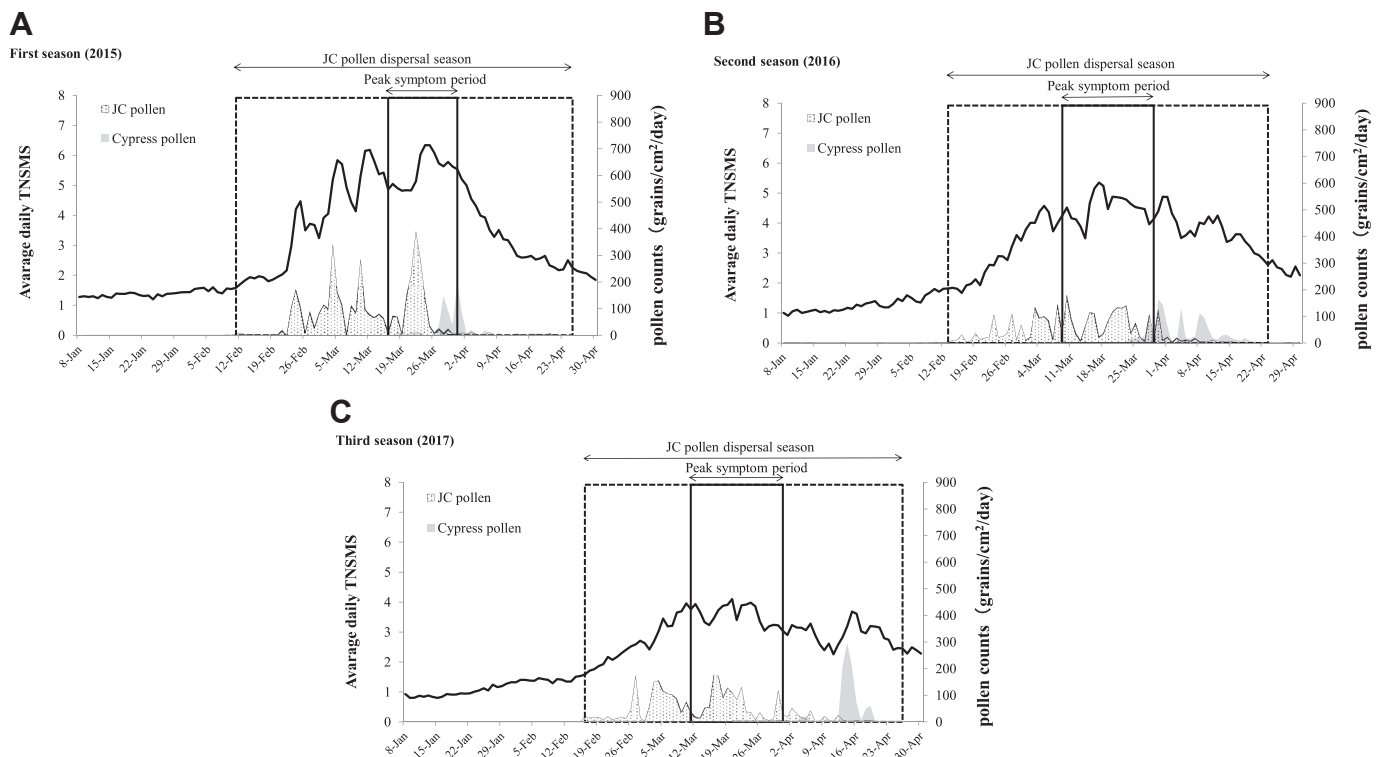


Fig. 2. Daily averaged TNSMS in the first (A), second (B), third (C), fourth (D), and fifth (E) pollen seasons. TNSMS, total nasal symptom and medication score; JC, Japanese cedar.

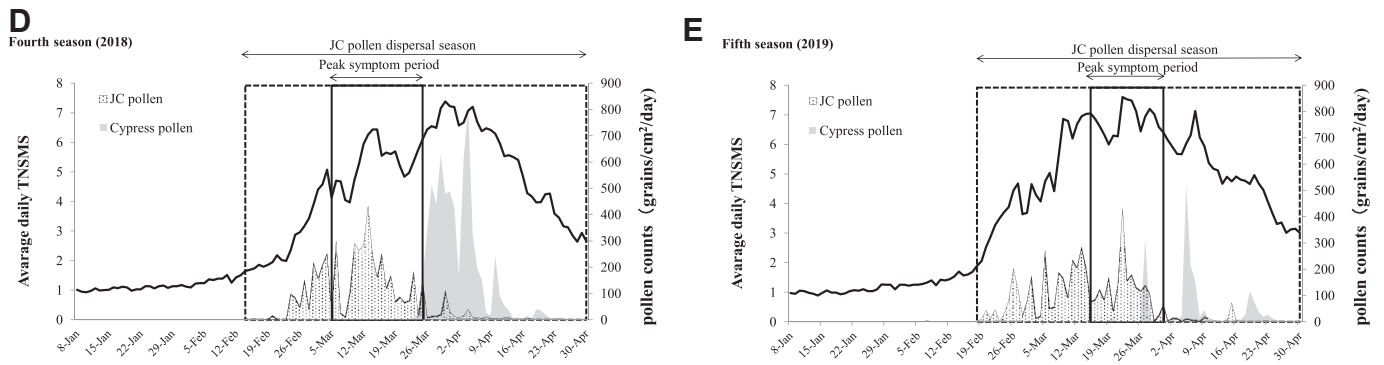


Fig. 2. (Continued)

experienced aphthous stomatitis and the second experienced oral edema, breathing difficulty, and nausea. The remaining 97.1% (134/138) of the ADRs were mild in severity. The majority of ADRs occurred within 4 weeks of treatment initiation (107; 77.5%) and subsided with time (Supplementary Fig. 1). Only two ADRs (in two patients) occurred after the first year of treatment. No ADRs were recorded in the 2-year post-treatment observation period.

Table 2

Symptom and medication scores (full analysis set).

Endpoint	1st season (2015) N = 219	2nd season (2016) N = 206	3rd season (2017) N = 193	4th season (2018) N = 182	5th season (2019) N = 171
Peak symptom period					
<i>Primary Endpoint</i>					
TNSMS	5.47 ± 3.38 (5.02–5.92)	4.52 ± 3.13 (4.09–4.95)	3.58 ± 2.63 (3.21–3.96)	5.28 ± 4.01 (4.69–5.87)	6.83 ± 4.65 (6.12–7.53)
<i>Individual symptom score</i>					
Sneezing	1.78 ± 0.89 (1.66–1.90)	1.54 ± 0.85 (1.42–1.66)	1.27 ± 0.81 (1.16–1.39)	1.73 ± 1.01 (1.58–1.87)	2.08 ± 1.13 (1.90–2.25)
Runny nose	1.95 ± 1.02 (1.82–2.09)	1.65 ± 0.95 (1.52–1.78)	1.35 ± 0.86 (1.23–1.47)	1.81 ± 1.11 (1.65–1.97)	2.20 ± 1.17 (2.02–2.37)
Blocked nose	1.27 ± 0.96 (1.14–1.40)	1.02 ± 0.91 (0.90–1.15)	0.80 ± 0.80 (0.69–0.91)	1.16 ± 1.07 (1.01–1.32)	1.54 ± 1.21 (1.36–1.72)
Itchy eyes	1.07 ± 0.80 (0.97–1.18)	0.86 ± 0.73 (0.76–0.96)	0.69 ± 0.67 (0.59–0.78)	1.10 ± 0.79 (0.98–1.21)	1.28 ± 0.91 (1.15–1.42)
Watery eyes	0.62 ± 0.66 (0.53–0.70)	0.52 ± 0.65 (0.43–0.61)	0.42 ± 0.58 (0.34–0.50)	0.64 ± 0.73 (0.53–0.75)	0.83 ± 0.85 (0.70–0.96)
<i>Individual medication score</i>					
Oral antihistamine	0.31 ± 0.71 (0.22–0.41)	0.19 ± 0.52 (0.12–0.26)	0.12 ± 0.42 (0.06–0.18)	0.39 ± 0.79 (0.28–0.51)	0.68 ± 1.03 (0.53–0.84)
Nasal spray	0.15 ± 0.51 (0.08–0.22)	0.11 ± 0.46 (0.05–0.18)	0.04 ± 0.24 (0.01–0.08)	0.19 ± 0.58 (0.11–0.28)	0.33 ± 0.79 (0.22–0.45)
Ocular antihistamine	0.25 ± 0.60 (0.17–0.33)	0.16 ± 0.53 (0.09–0.24)	0.09 ± 0.33 (0.04–0.14)	0.32 ± 0.70 (0.22–0.42)	0.48 ± 0.90 (0.34–0.61)
<i>Combined score</i>					
TNSS	5.01 ± 2.60 (4.66–5.35)	4.21 ± 2.51 (3.87–4.55)	3.42 ± 2.25 (3.10–3.74)	4.70 ± 2.99 (4.26–5.13)	5.81 ± 3.25 (5.32–6.30)
TOSS	1.69 ± 1.37 (1.51–1.87)	1.38 ± 1.31 (1.20–1.56)	1.11 ± 1.18 (0.94–1.28)	1.74 ± 1.45 (1.52–1.95)	2.11 ± 1.67 (1.86–2.37)
TNOSS	6.69 ± 3.74 (6.20–7.19)	5.59 ± 3.59 (5.10–6.09)	4.53 ± 3.19 (4.08–4.99)	6.43 ± 4.25 (5.81–7.05)	7.92 ± 4.64 (7.22–8.62)
TNOMS	0.71 ± 1.50 (0.51–0.91)	0.47 ± 1.22 (0.30–0.64)	0.25 ± 0.75 (0.15–0.36)	0.91 ± 1.76 (0.65–1.16)	1.49 ± 2.28 (1.15–1.84)
TOSMS	1.94 ± 1.80 (1.70–2.18)	1.55 ± 1.69 (1.32–1.78)	1.20 ± 1.42 (1.00–1.40)	2.06 ± 2.02 (1.76–2.35)	2.59 ± 2.42 (2.23–2.96)
TNOSMS	7.40 ± 4.87 (6.75–8.05)	6.06 ± 4.51 (5.44–6.68)	4.78 ± 3.73 (4.25–5.31)	7.34 ± 5.74 (6.50–8.18)	9.42 ± 6.65 (8.41–10.42)
JC pollen dispersal season					
<i>Individual symptom score</i>					
Sneezing	1.30 ± 0.62 (1.22–1.39)	1.30 ± 0.70 (1.20–1.39)	1.10 ± 0.67 (1.01–1.19)	1.51 ± 0.79 (1.40–1.63)	1.67 ± 0.90 (1.53–1.80)
Runny nose	1.44 ± 0.73 (1.35–1.54)	1.38 ± 0.79 (1.27–1.48)	1.15 ± 0.73 (1.05–1.25)	1.61 ± 0.88 (1.48–1.73)	1.75 ± 0.98 (1.61–1.90)
Blocked nose	0.88 ± 0.68 (0.79–0.97)	0.81 ± 0.72 (0.71–0.91)	0.65 ± 0.68 (0.55–0.74)	1.04 ± 0.86 (0.91–1.16)	1.15 ± 0.95 (1.01–1.30)
Itchy eyes	0.72 ± 0.56 (0.65–0.80)	0.67 ± 0.60 (0.59–0.76)	0.56 ± 0.58 (0.48–0.65)	0.85 ± 0.62 (0.76–0.94)	0.94 ± 0.71 (0.83–1.05)
Watery eyes	0.40 ± 0.45 (0.34–0.47)	0.39 ± 0.51 (0.32–0.46)	0.33 ± 0.47 (0.26–0.39)	0.51 ± 0.56 (0.43–0.59)	0.58 ± 0.64 (0.49–0.68)
<i>Individual medication score</i>					
Oral antihistamine	0.16 ± 0.38 (0.11–0.22)	0.14 ± 0.39 (0.08–0.19)	0.09 ± 0.29 (0.05–0.13)	0.33 ± 0.58 (0.25–0.41)	0.43 ± 0.71 (0.32–0.54)
Nasal spray	0.10 ± 0.31 (0.06–0.14)	0.07 ± 0.29 (0.03–0.11)	0.04 ± 0.22 (0.01–0.07)	0.19 ± 0.45 (0.12–0.25)	0.20 ± 0.49 (0.13–0.27)
Ocular antihistamine	0.16 ± 0.38 (0.11–0.21)	0.12 ± 0.36 (0.07–0.17)	0.08 ± 0.28 (0.04–0.12)	0.24 ± 0.50 (0.17–0.31)	0.30 ± 0.60 (0.21–0.39)
<i>Combined score</i>					
TNSMS	3.89 ± 2.24 (3.59–4.19)	3.69 ± 2.44 (3.36–4.03)	3.03 ± 2.17 (2.72–3.33)	4.67 ± 3.05 (4.22–5.12)	5.21 ± 3.51 (4.68–5.74)
TNSS	3.63 ± 1.83 (3.38–3.87)	3.49 ± 2.04 (3.20–3.77)	2.90 ± 1.88 (2.63–3.17)	4.15 ± 2.33 (3.81–4.49)	4.58 ± 2.60 (4.18–4.97)
TOSS	1.13 ± 0.96 (1.00–1.26)	1.06 ± 1.05 (0.92–1.21)	0.89 ± 1.00 (0.75–1.03)	1.36 ± 1.12 (1.20–1.53)	1.53 ± 1.28 (1.33–1.72)
TNOSS	4.76 ± 2.61 (4.41–5.10)	4.55 ± 2.92 (4.15–4.95)	3.79 ± 2.70 (3.41–4.17)	5.52 ± 3.29 (5.04–6.00)	6.10 ± 3.67 (5.55–6.66)
TNOMS	0.42 ± 0.88 (0.30–0.54)	0.33 ± 0.83 (0.21–0.44)	0.21 ± 0.60 (0.12–0.29)	0.76 ± 1.25 (0.57–0.94)	0.93 ± 1.52 (0.70–1.16)
TOSMS	1.29 ± 1.25 (1.12–1.46)	1.18 ± 1.31 (1.00–1.36)	0.97 ± 1.20 (0.80–1.14)	1.60 ± 1.52 (1.38–1.83)	1.83 ± 1.78 (1.56–2.10)
TNOSMS	5.18 ± 3.27 (4.74–5.61)	4.87 ± 3.54 (4.39–5.36)	4.00 ± 3.13 (3.55–4.44)	6.27 ± 4.35 (5.64–6.91)	7.03 ± 5.00 (6.28–7.79)

Data are presented as the mean ± SD (95% CI). CI, confidence interval; JC, Japanese cedar; SD, standard deviation; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TNOSS, total nasal and ocular symptom score; TNOMS, total nasal and ocular medication score; TNSMS, total nasal symptom and medication score; TOSMS, total ocular symptom and medication score; TNOSMS, total nasal and ocular symptom and medication score.

Table 3

Symptom relief evaluation (full analysis set).

Evaluation	1st season (2015) N = 219	2nd season (2016) N = 206	3rd season (2017) N = 193	4th season (2018) N = 182	5th season (2019) N = 171
<i>Peak symptom period</i>					
Participants with no use of rescue medications†	64.8 (58.5–71.2)	75.2 (69.3–81.1)	80.3 (74.7–85.9)	63.7 (56.8–70.7)	50.3 (42.8–57.8)
Well-days‡	34.96 ± 37.02 (30.03–39.89)	46.18 ± 36.47 (41.17–51.19)	56.78 ± 38.31 (51.34–62.22)	39.66 ± 36.72 (34.29–45.03)	29.38 ± 35.74 (23.99–34.78)
Severe symptom days‡	20.65 ± 30.76 (16.55–24.75)	14.30 ± 26.37 (10.68–17.92)	8.87 ± 21.10 (5.87–11.87)	21.89 ± 32.90 (17.08–26.70)	33.53 ± 39.14 (27.62–39.44)
TNSMS < 3†	23.3 (17.7–28.9)	37.4 (30.8–44.0)	47.7 (40.6–54.7)	33.5 (26.7–40.4)	18.7 (12.9–24.6)
<i>JC pollen dispersal season</i>					
Participants with no use of rescue medications†	56.6 (50.1–63.2)	68.9 (62.6–75.3)	75.1 (69.0–81.2)	47.8 (40.5–55.1)	45.0 (37.6–52.5)
Well-days‡	54.12 ± 28.90 (50.27–57.97)	57.44 ± 31.02 (53.18–61.70)	65.87 ± 31.32 (61.42–70.32)	49.14 ± 29.63 (44.81–53.47)	43.32 ± 32.35 (38.43–48.20)
Severe symptom days‡	11.88 ± 18.33 (9.44–14.32)	10.07 ± 18.64 (7.51–12.63)	6.45 ± 15.00 (4.33–8.58)	18.61 ± 24.23 (15.07–22.16)	22.33 ± 28.19 (18.08–26.59)

Data are presented as the mean ± SD (95% CI), except † mean (95% CI).

CI, confidence interval; JC, Japanese cedar; SD, standard deviation; TNSMS, total nasal symptom and medication score.

† Well days are those in which all symptoms (runny nose, blocked nose, sneezing, itchy eyes, and watery eyes) are evaluated as – or 1+ and no rescue medications are used.

‡ Severe symptom days are those with at least one symptom evaluated as 4+ for nasal symptoms or 3+ for ocular symptoms.

9 months of treatment, plateaued until the end of the treatment period, and decreased during the 2-year observation period. Nevertheless, JC pollen-specific IgG4 levels were still higher in the post-treatment period (measured immediately before the fourth and fifth JC pollen dispersal seasons) than in the pretreatment level (Fig. 3B). The change in the ratio of JC pollen-specific IgE to JC pollen-specific IgG4 level was similar to the change in JC pollen-specific IgE level (Fig. 3C). Seasonal cycling of the JC pollen-specific IgE and IgG4 levels was

observed, with both levels increasing during the dispersal seasons and then decreasing until the following pollen dispersal season.

Figure 3D–F shows changes in the levels of JC pollen-specific IgE, IgG4, and IgE:IgG4 ratio for patients who did and did not experience ADRs. The specific IgE and IgG4 levels tended to be slightly higher among patients who experienced ADRs compared with those who did not; however, the differences were not significant.

Table 4

JRQLQ evaluation (full analysis set).

	1st season (2015) N = 219	2nd season (2016) N = 204	3rd season (2017) N = 193	4th season (2018) N = 181	5th season (2019) N = 171
a) Evaluated on March 15					
<i>General state†</i>					
0 Fine	6 (2.7)	10 (4.9)	24 (12.4)	6 (3.3)	6 (3.5)
1	35 (16.0)	73 (35.8)	71 (36.8)	48 (26.5)	30 (17.6)
2	87 (39.7)	49 (24.0)	65 (33.7)	40 (22.1)	49 (28.8)
3	74 (33.8)	61 (29.9)	29 (15.0)	70 (38.7)	65 (38.2)
4 Crying	17 (7.8)	11 (5.4)	4 (2.1)	17 (9.4)	20 (11.8)
<i>Individual component score‡</i>					
Usual daily activities	1.19 ± 1.02	0.97 ± 1.01	0.61 ± 0.80	1.10 ± 1.08	1.38 ± 1.12
Outdoor activities	1.33 ± 1.20	1.07 ± 1.16	0.74 ± 0.96	1.26 ± 1.26	1.57 ± 1.28
Social functioning	0.85 ± 0.94	0.67 ± 0.90	0.47 ± 0.79	0.83 ± 1.01	1.12 ± 1.11
Impaired sleeping	1.16 ± 1.23	0.82 ± 0.98	0.62 ± 0.97	1.07 ± 1.19	1.36 ± 1.27
Physical problems	1.29 ± 1.18	1.10 ± 1.14	0.65 ± 0.92	1.12 ± 1.19	1.41 ± 1.25
Emotional functions	1.20 ± 1.13	0.85 ± 1.04	0.56 ± 0.88	0.99 ± 1.14	1.28 ± 1.20
b) Evaluated on March 31					
<i>General state†</i>					
0 Fine	15 (6.8)	16 (7.8)	25 (13.0)	7 (3.9)	10 (5.8)
1	42 (19.2)	63 (30.9)	76 (39.6)	18 (10.0)	34 (19.9)
2	78 (35.6)	61 (29.9)	59 (30.7)	45 (25.0)	41 (24.0)
3	64 (29.2)	56 (27.5)	24 (12.5)	79 (43.9)	56 (32.7)
4 Crying	20 (9.1)	8 (3.9)	8 (4.2)	31 (17.2)	30 (17.5)
<i>Individual component score‡</i>					
Usual daily activities	1.20 ± 1.07	0.95 ± 1.00	0.59 ± 0.83	1.40 ± 1.13	1.44 ± 1.21
Outdoor activities	1.25 ± 1.27	1.09 ± 1.17	0.71 ± 0.95	1.60 ± 1.35	1.57 ± 1.36
Social functioning	0.88 ± 0.96	0.70 ± 0.90	0.48 ± 0.80	1.12 ± 1.15	1.18 ± 1.22
Impaired sleeping	1.10 ± 1.12	0.84 ± 1.03	0.62 ± 1.00	1.46 ± 1.36	1.32 ± 1.31
Physical problems	1.26 ± 1.20	1.00 ± 1.12	0.66 ± 0.97	1.51 ± 1.31	1.46 ± 1.36
Emotional functions	1.15 ± 1.18	0.84 ± 1.01	0.55 ± 0.85	1.28 ± 1.23	1.31 ± 1.28

Data are presented as † N (%), or ‡ mean ± SD.

JRQLQ, Japanese Rhinoconjunctivitis Quality of Life Questionnaire; SD, standard deviation.

Table 5

Summary of adverse events and adverse drug reactions.

	Adverse events			Adverse drug reactions		
	E	N	%	E	N	%
Serious AEs	21	16	6.9	0	0	0.0
All AEs	1537	203	87.1	138	73	31.3
Mild	1505	202	86.7	134	73	31.3
Moderate	31	24	10.3	4	2	0.9
Severe	1	1	0.4	0	0	0.0
AEs leading to discontinuation	14	6	2.6	12	4	1.7

AE, adverse event; E, number of AEs or adverse drug reactions; N, number of participants with AEs or adverse drug reactions; %, percentage of participants with AEs or adverse drug reactions.

Discussion

This was an open-label trial examining the efficacy, safety, and post-treatment effect persistence of JC pollen SLIT drops in patients with JC pollinosis. Participants were treated with JC pollen SLIT drops for approximately 33 months and then observed for the following 2 years.

The primary endpoint, TNSMS during the peak symptom period, decreased steadily from the first to the third pollen dispersal seasons. In a previous clinical trial of JC pollen SLIT drops, TNSMS was 18% and 30% lower in the treatment group than in the placebo group during the peak symptom periods in years 1 and 2 of treatment, respectively.¹¹ Clinical trials of JC pollen SLIT tablets have also reported a duration-dependent increase in efficacy over a 3-year treatment period.^{17,18} The results of the present trial are thus in line with previous studies showing a treatment duration-dependent effect of SLIT on TNSMS during the 3-year treatment period.

Several studies have demonstrated effect persistence after SLIT therapy in patients with seasonal allergic rhinitis who were treated for 3 and observed for an additional 2 years.^{13,14} We are also investigating the effects of JC pollen SLIT tablets (2000 JAU) in JC pollinosis patients from the same region of Japan in a placebo-controlled trial performed concurrently with the present study. In that trial, the TNSMS in the first season (2015) was 5.49, which was significantly (21.4%, $p < 0.001$) lower than that seen in the placebo group.¹⁷ This score is comparable to that observed in 2015 in the present study (5.47), supporting a significant treatment effect of JC pollen SLIT drops in the present study despite the lack of a placebo control group.

JC pollen counts can vary greatly from year to year and will thus affect the efficacy of SLIT. In the present study, we observed higher JC pollen counts during the symptom peak period of 2018 compared with 2015, 2016, and 2017 (3343.2 vs 1472.5, 1569.0, and 1359.7 grains/cm², respectively), yet the TNSMS for 2018 (5.28) was still lower than that in 2015 (5.47), suggesting that the treatment effect persisted at least into the fourth season. Nevertheless, the TNSMS increased to 6.83 in 2019, despite a lower JC pollen count (2096 grains/cm²), indicating that the duration of the treatment effect may decrease over time.

The percentage of “well days” and “severe symptom days” during the peak symptom periods, both endpoints with clinical significance, were 56.78% and 8.87%, respectively, in the third season, 39.66% and 21.89% in the fourth season, and 29.38% and 33.53% in the fifth season. These changes are consistent with the trends in TNSMS, the primary endpoint.

The World Allergy Organization considers a $\geq 20\%$ decrement in symptom and medication scores between placebo and active drug groups to be clinically significant.²² However, there has been no international consensus regarding treatment goals for allergen-

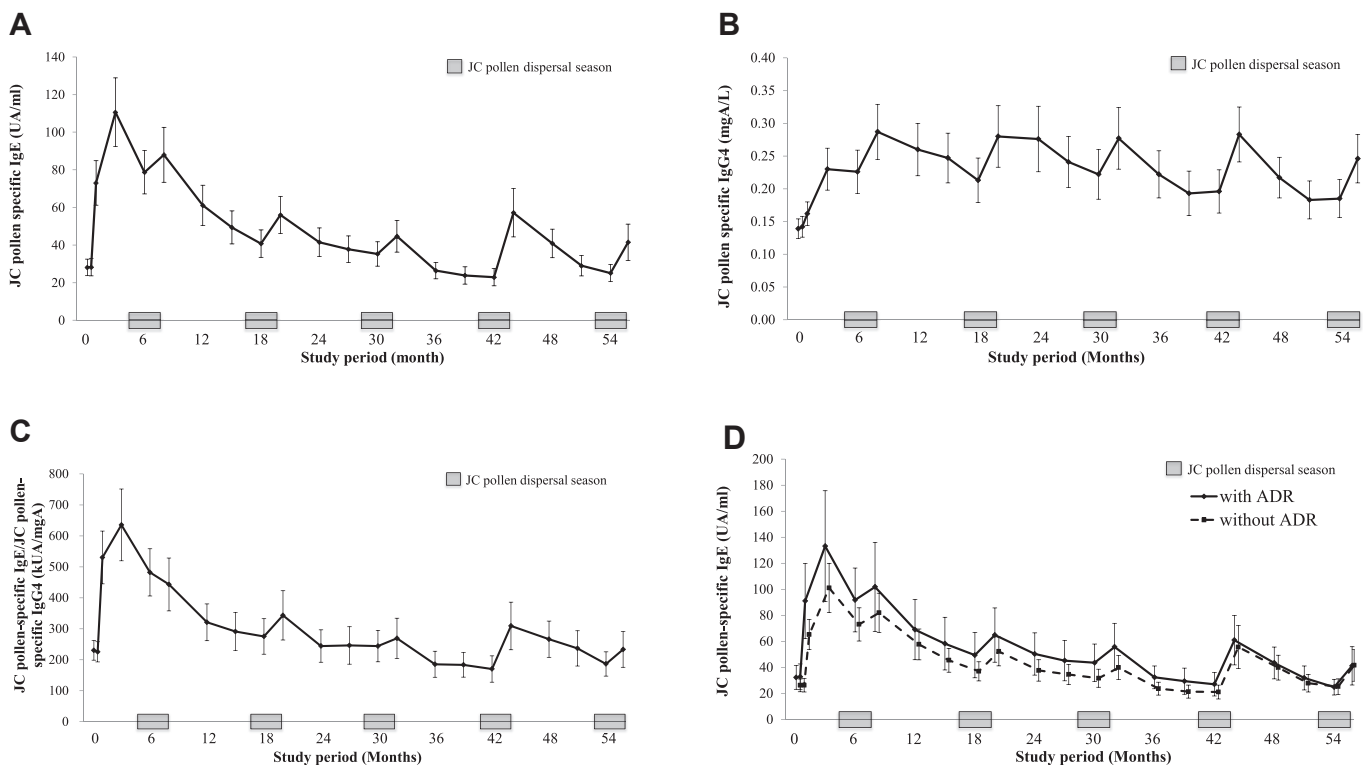


Fig. 3. Serum levels of JC pollen-specific IgE (A) and JC pollen-specific IgG4 (B), and the ratio of JC pollen-specific IgE to JC pollen-specific IgG4 level (C). The same measurements are shown separately for patients with and without adverse drug reactions in (D), (E), and (F), respectively. The first through the fifth JC pollen seasons started approximately 6, 18, 30, 42, and 54 months, respectively, after treatment initiation. JC, Japanese cedar.

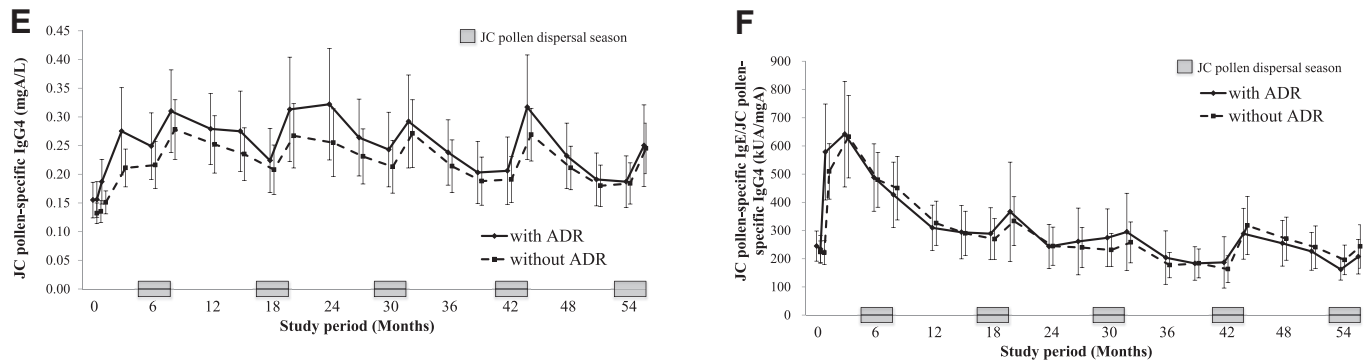


Fig. 3. (Continued)

specific immunotherapy in clinical practice. The Japanese guidelines for allergic rhinitis⁵ cite “a state in which no symptoms or very mild symptoms that affect daily life are present, and no medication is necessary” as a treatment goal. In the present study, the use of masks and goggles to protect against JC pollen was prohibited. Therefore, under these conditions, we considered “the percentage of participants who did not use rescue medication during the peak symptom period” and “the percentage of participants during the same period, whose mean TNSMS values were less than 3” to be clinically significant endpoints for the evaluation of the effect persistence of JC pollen SLIT drops. The percentage of participants who did not use rescue medication during the peak symptom period of the fourth and fifth seasons was 63.7% and 50.3%, respectively, compared with percentages between 64.8 and 80.3% during the 3-year treatment period. We consider these findings to reflect effect persistence. Consistent with this, 33.5% and 18.7% of the participants had mean TNSMS values of <3 during the peak symptom periods of the fourth and fifth seasons, respectively.

We assessed QOL by administering the JRQLQ on March 15 and 31 of each year. This questionnaire assesses the patient's QOL over the preceding 2 weeks. We found that the QOL scores were comparable on both dates for the first three seasons and reflected a consistent annual improvement. In 2018, however, the QOL was worse for the March 31 assessment than the March 15 assessment, which we believe was a consequence of the unusually high levels of cypress pollen dispersal in late March of that year. Of note, we consider the similarity between the QOL profiles assessed on March 15 of the fourth and first seasons to be evidence of effect persistence. Nevertheless, because the QOL scores were worse in the fifth season than in the first season, the effects may not be durable. These changes in QOL mirror those observed for the primary endpoint (TNSMS).

Our study has some limitations. This was an open-label trial without a control or placebo group, and the results should be verified in a placebo-controlled, double-blind clinical trial. As mentioned, a double-blind comparative trial of JC pollen SLIT tablets with the same treatment regimen is underway, and the results as of the third year of the trial have been reported.^{17,18} Data from the 2-year post-treatment observation period of that trial should help to elucidate the true effect persistence of SLIT in JC pollinosis patients.

To our knowledge, this is the first trial to track longitudinal changes in immunological parameters in JC pollinosis patients during 3 years of SLIT and 2 years of observation. The changes observed in the present study suggest that JC pollen SLIT drops initially increase the production of JC pollen-specific IgE and then induce a shift toward the production of JC pollen-specific IgG4. JC

pollinosis is thought to involve an antigen-specific Th2-dominant immune response, suggesting that SLIT may induce immunodeviation or tolerance.

Nearly all of the ADRs observed in this study were mild in severity and occurred within 2 months of treatment initiation, which is in line with the results of previous trials of JC pollen SLIT drops¹¹ and supports the safety of long-term treatment.

In conclusion, this clinical trial of JC pollen SLIT drops in Japanese JC pollinosis patients demonstrated treatment duration-dependent efficacy and continued alleviation of symptoms, reduction in pharmacotherapy use, and improvement in quality of life during the 2-year period after cessation of treatment. Furthermore, the safety profile over the entire 5-year study period was favorable.

Acknowledgements

This trial was funded by Torii, Tokyo, Japan. The authors thank the patients who participated in this study and their family members as well as the investigators and site staff. We also thank the clinical trial team at Torii for clinical project management, operational oversight, quality control, safety monitoring, data management, and statistical analysis. Finally, the authors would like to thank Editage (www.editage.jp) and Anne M. O'Rourke, PhD, from Edanz Group (www.edanzediting.co.jp) for editing drafts of this manuscript. Writing assistance was funded by Torii.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.05.008>.

Conflict of interest

YN received honoraria from Meiji-seika Pharma. KO received honoraria from Torii, Taiho, and Mitsubishi Tanabe, and a writing fee from Torii. YO received honoraria from Torii, Shionogi, Kyorin, Taiho, and Mitsubishi Tanabe, and research funding from Kyorin and Yamada Bee Farm. ShK, SaK, and YT are employed by Torii. The rest of the authors have no conflict of interest.

Authors' contributions

KO and YO designed the trial. YN, TN, SS, HK, and NI were the principal investigators and contributed to the conduct of the study and data collection. ShK and SaK managed the study and interpreted the data. YT performed the statistical analysis. All authors were involved in the manuscript review and approved the final content.

References

1. Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis: the national affliction. *J Allergy Clin Immunol* 2014;**133**:632–9. e635.
2. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003;**91**:288–96.
3. Kaneko Y, Motohashi Y, Nakamura H, Endo T, Eboshida A. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. *Int Arch Allergy Immunol* 2005;**136**:365–7.
4. Okamoto Y, Horiguchi S, Yamamoto H, Yonekura S, Hanazawa T. Present situation of cedar pollinosis in Japan and its immune responses. *Allergol Int* 2009;**58**:155–62.
5. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int* 2017;**66**:205–19.
6. Sakashita M, Hirota T, Harada M, Nakamichi R, Tsunoda T, Osawa Y, et al. Prevalence of allergic rhinitis and sensitization to common aeroallergens in a Japanese population. *Int Arch Allergy Immunol* 2010;**151**:255–61.
7. Urashima M, Asaka D, Endo T, Omae S, Sugimoto N, Takaishi S, et al. Japanese cedar pollinosis in Tokyo residents born after massive national afforestation policy. *Allergy* 2018;**73**:2395–7.
8. Horiguchi S, Okamoto Y, Yonekura S, Okawa T, Yamamoto H, Kunii N, et al. A randomized controlled trial of sublingual immunotherapy for Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2008;**146**:76–84.
9. Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, et al. A randomized double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol Int* 2008;**57**:265–75.
10. Fujimura T, Yonekura S, Horiguchi S, Taniguchi Y, Saito A, Yasueda H, et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clin Immunol* 2011;**139**:65–74.
11. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2015;**166**:177–88.
12. Yuta A, Ogawa Y, Suzuki H, Ogihara H, Kozaki H, Ohta N, et al. [Clinical efficacy of sublingual immunotherapy in a large amount of pollen dispersal and its impact of treatment year]. *Arerugi* 2018;**67**:1011–9 (in Japanese).
13. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;**129**:717–25.
14. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy* 2015;**5**:12.
15. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010;**126**:969–75.
16. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;**114**:851–7.
17. Gotoh M, Yonekura S, Imai T, Kaneko S, Horikawa E, Konno A, et al. Long-term efficacy and dose-finding trial of Japanese cedar pollen sublingual immunotherapy tablet. *J Allergy Clin Immunol Pract* 2019;**7**:1287–97.
18. Yonekura S, Gotoh M, Kaneko S, Kanazawa K, Takeuji Y, Okubo K, et al. Treatment duration-dependent efficacy of Japanese cedar pollen sublingual immunotherapy: evaluation of a phase II/III trial over three pollen dispersal seasons. *Allergol Int* 2019;**68**:494–505.
19. Roberts G, Pfaar O, Akdis CA, Ansotegui JJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;**73**:765–98.
20. Gotoh M, Okubo K, Okamoto Y, Yonekura S, Kaneko S, Konno A. [Investigation of treatment goal in allergen immunotherapy for Japanese cedar pollinosis – based on the results of the TO-194SL (CEDARTOLEN cedar pollen sublingual droplet) phase III clinical trial]. *Arerugi* 2018;**67**:938–47 (in Japanese).
21. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract* 2017;**5**:58–62.
22. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;**7**:6.

Supplementary Materials

Supplementary Table 1 Rhinitis symptom evaluation and scores

Symptom	4	3	2	1	0
Runny nose	≥21 times	11–20 times	6–10 times	1–5 times	0
Sneezing	≥21 times	11–20 times	6–10 times	1–5 times	0
Blocked nose	Completely obstructed all day	Very severe nasal blockage causing prolonged oral breathing in a day	Severe nasal blockage causing occasional oral breathing in a day	Nasal blockage without oral breathing	No trouble

Supplementary Table 2 Conjunctivitis symptom evaluation and scores

Symptom	3	2	1	0
Itchy eyes	Intolerably itchy	Very itchy	Slightly itchy	No trouble
Watery eyes	Cannot do regular tasks	Very watery	Not very watery	No trouble

Supplementary Table 3 Components of composite scores

	TNSS	TOSS	TNOSS	TNOMS	TNSMS	TOSMS	TNOSMS
Runny nose	0-4	--	0-4	--	0-4	--	0-4
Sneezing	0-4	--	0-4	--	0-4	--	0-4
Blocked nose	0-4	--	0-4	--	0-4	--	0-4
Itchy eyes	--	0-3	0-3	--	--	0-3	0-3
Watery eyes	--	0-3	0-3	--	--	0-3	0-3
Oral antihistamine	--	--	--	0 or 3	0 or 3	--	0 or 3
Nasal spray	--	--	--	0 or 3	0 or 3	--	0 or 3
Ocular antihistamine	--	--	--	0 or 3	--	0 or 3	0 or 3
Total	0-12	0-6	0-18	0-9	0-18	0-9	0-27

TNSS, total nasal symptom score; TOSS, total ocular symptom score; TNOSS, total

nasal and ocular symptom score; TNOMS, total nasal and ocular medication score;

TNSMS, total nasal symptom and medication score; TOSMS, total ocular symptom and

medication score; TNOSMS, total nasal and ocular symptom and medication score.

Supplementary Table 4 JC pollen counts and evaluation periods

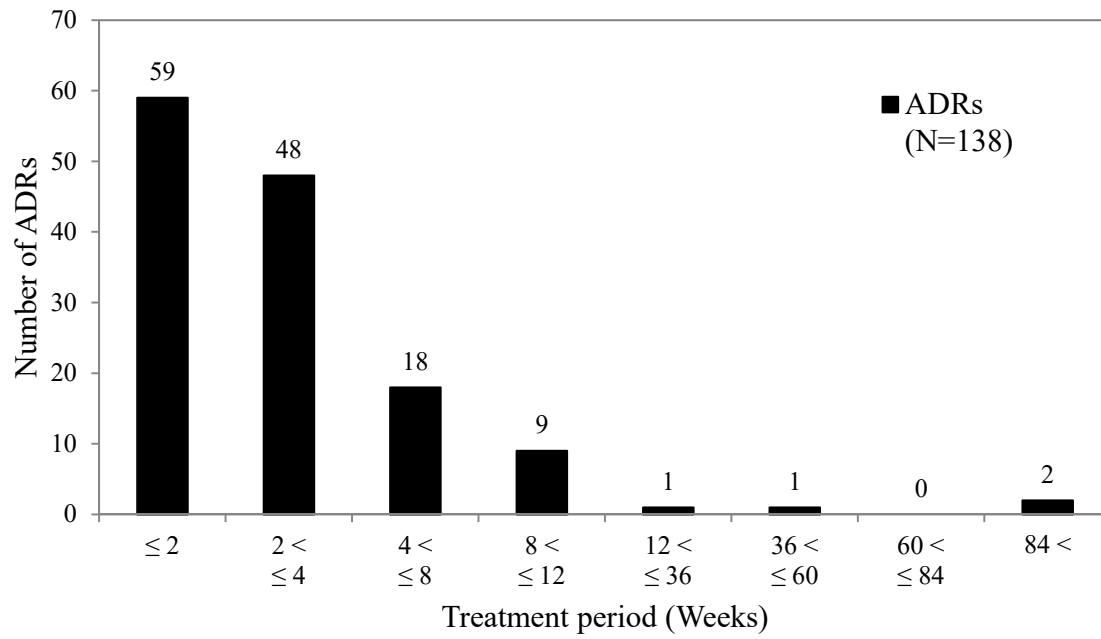
Year	JC pollen dispersal season (JC pollen counts)	Peak symptom period (JC pollen counts)
2015	February 11 to April 25 (3892.4 grains/cm ²)	March 16 to March 31 (1472.5 grains/cm ²)
2016	February 13 to April 23 (2994.0 grains/cm ²)	March 9 to March 29 (1569.0 grains/cm ²)
2017	February 16 to April 26 (2894.1 grains/cm ²)	March 11 to March 31 (1359.1 grains/cm ²)
2018	February 14 to April 30 (5015.9 grains/cm ²)	March 5 to March 25 (3343.2 grains/cm ²)
2019	February 18 to April 30 (4960.1 grains/cm ²)	March 15 to March 31 (2096.0 grains/cm ²)

JC, Japanese cedar.

Supplementary Table 5 Incidence of adverse events and adverse drug reactions according to patient characteristics

	N	Adverse events	Adverse drug reactions
		no. (%)	no. (%)
<i>Age (y)</i>			
12 to 19	20	19 (95.0%)	5 (25.0%)
20 to 29	52	43 (82.7%)	19 (36.5%)
30 to 39	54	50 (92.6%)	21 (38.9%)
40 to 49	82	66 (80.5%)	21 (25.6%)
50 to 64	25	25 (100.0%)	7 (28.0%)
<i>Years with JC pollinosis</i>			
<5	12	12 (100.0%)	6 (50.0%)
≥5 to <10	36	26 (72.2%)	8 (22.2%)
≥10 to <15	59	54 (91.5%)	22 (37.3%)
≥15 to <20	50	46 (92.0%)	14 (28.0%)
≥20	76	65 (85.5%)	23 (30.3%)
<i>JC pollen-specific IgE (UA/mL)</i>			
≥3.5 to <17.5	120	100 (83.3%)	27 (22.5%)
≥17.5 to <50	73	67 (91.8%)	33 (45.2%)
≥50 to <100	32	28 (87.5%)	10 (31.3%)
≥100	8	8 (100.0%)	3 (37.5%)

N, number of participants in each group; no., number of participants with adverse events or adverse drug reactions; %, percentage of participants with adverse events or adverse drug reactions; JC, Japanese cedar.



Supplementary Figure 1 Time of occurrence of ADRs.

Cumulative number of adverse drug reaction (ADRs) from the first day of treatment to the indicated number of weeks.