NPMCs from patients with NECRS and those with ECRS; however, the elevated IL-5 and IL-9 production that was induced by treatment with IL-25 occurred only in NPMCs from patients with ECRS (Fig 6B). The present findings suggest that not only the numbers but also the reactivities to IL-25 differ in memory T_H2 and T_H9 cells between these cells from patients with NECRS and those with ECRS. A subpopulation of memory T_H2 and T_H9 cells expressing IL-17RB might promote chronic eosinophilic inflammation in patients with CRSwNP and cause differences in pathogenesis between ECRS and NECRS, because the IL-17RB level of tissue memory $CD4^+$ T cells correlated with the number of infiltrating eosinophils and CT score, respectively (Fig 5B).

Interleukin-25 was first described as a cytokine produced by mouse T_H2 cells.[14] Epithelial cells, eosinophils, mast cells, and endothelial cells express IL-25 in patients with allergic diseases.[20,21] In the present study, epithelial cells, mast cells, and eosinophils expressed IL-25 in NPs (Fig 2). A few mast cells in NPs expressed IL-25, although the major source of IL-25 in ECRS was most likely eosinophils based on the large numbers of $IL\text{-}25^+$ ECP^+ cells. IL-25 levels were significantly increased and were correlated with IL-5 and IL-9 levels in ECRS samples but not in NECRS samples (Fig 1). Moreover, IL-25 levels in NPs were significantly correlated with the number of tissue eosinophils and CT scores. Accordingly, acting with IL-17RB–expressing T_H2 cells, IL-25 could induce a vicious cycle that accelerates eosinophil infiltration. However, immunofluorescence analyses did not show any significant difference in IL-25 expression by epithelial cells between patients with NECRS and those with ECRS. In patients with asthma, although IL-25 was expressed by most epithelial cells in the bronchial mucosa, IL-25 expression by epithelial cells was not increased by allergen challenge.[21] These effects might depend on an IL-25–releasing factor[39] or on the existence and sensitivity of IL-17RB–expressing cells, such as the T_H2 and T_H9 cells investigated in this study.

Atopic status might be involved in the development of eosinophilic inflammation in patients with CRSwNP.[40,41] However, several clinical and pathologic features of CRSwNP are related to the classification of the grade of eosinophil infiltration (Table 1, Fig 5). The present results indicated that activating pathogenic tissue memory T_H2 and T_H9 cells in NPs could exacerbate chronic local eosinophilic inflammation regardless of atopic status. Clinically, a relation was found between ECRS and late-onset or aspirin-intolerant asthma (Table 1). Late-onset asthma is not related to atopy and its relation with ECRS is consistent with the features of CRSwNP observed in a large European study.[42,43] From the perspective of eosinophilic airway comorbidity, pathogenic memory T_H2 and T_H9 cells with similar properties could contribute to the onset and exacerbation of late-onset asthma. This possibility is supported by findings that *IL-17RB* gene polymorphisms affected the sensitivity of individuals with asthma.[44]

In conclusion, this study provides new information on a subpopulation of tissue memory $CD4^+$ T cells and on the functional significance of local T cells and IL-25 in human NPs. IL-25 and memory T_H2 and T_H9 cells that express IL-17RB could contribute to eosinophil infiltration in CRSwNP and could be the difference between NECRS and ECRS. Further studies will be required to clarify the detailed roles of IL-25 in eosinophilic inflammation and the mechanisms of differentiation and development of pathogenic memory T_H2 cells that express high IL-17RB levels, which could provide new treatment strategies for eosinophilic airway diseases.

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Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis

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ABSTRACT

Background: Japanese cedar (JC) pollinosis is the most common seasonal allergic rhinitis in Japan. Standardised JC pollen extract is available for subcutaneous immunotherapy, but this treatment is limited by potentially serious side effects. The aim of the double-blind, randomised comparative study was to evaluate the efficacy and safety of standardised JC pollen extract in a new oral formulation (CEDARTOLEN®, Torii Pharmaceutical Co. Ltd, Tokyo, Japan) for sublingual immunotherapy (SLIT) for JC pollinosis.

Methods: A total of 531 subjects with JC pollinosis were randomised into two groups at a ratio of 1:1 to receive daily sublingual administration of standardised JC pollen extract with a maintenance dose of 2000 Japanese allergy units (JAU) or placebo for two consecutive pollen seasons. The efficacy was evaluated using the total nasal symptom and medication score (TNSMS) as the primary endpoint. Secondary endpoints included the total ocular symptom and medication score (TOSMS), and scores for individual symptoms and medication.

Results: The TNSMS was significantly lower ($p < 0.0001$) in the SLIT group compared with the placebo group in the peak symptom period by 18% and 30% in the first and second seasons, respectively. All secondary endpoints were also significantly lower in the SLIT group in both seasons. No systemic anaphylaxis occurred in the study.

Conclusions: SLIT with daily administration of standardized JC pollen extract was effective for improving nasal and ocular symptoms of JC pollinosis and reducing use of relief medication. The JC pollen extract was well tolerated with only local adverse events.

INTRODUCTION

In recent years, many countries have had an increase in the prevalence of allergic rhinitis. In Japan, Japanese cedar (JC; *Cryptomeria japonica D. Don*) pollen is the most important causal allergen of pollinosis. Cedar forests cover nearly 12% of the total land area of Japan, and produce a large amount of pollen every year. ~~and, in contrast to grass pollen, which spreads less than 100 m,~~ Cedar pollen can travel a long distance and reach major cities, including Tokyo and Osaka, causing wide-spread pollinosis [1-5]. Cedar pollen dispersal usually starts in early February and lasts for 10 weeks in the Tokyo area. This is followed by Japanese cypress pollen dispersal, which reaches a peak in early April. JC pollinosis is estimated to affect more than a quarter of the total Japanese population [6].

Treatment of JC pollinois is similar to that for other pollinosis; that is, symptomatic treatment with antihistamines and nasal corticosteroids. However, this treatment only gives relief from symptoms, and does not modify or cure the disease. In contrast, allergen-specific immunotherapy can change the course of the disease. Subcutaneous immunotherapy (SCIT) has been used for JC pollinosis, but is limited by potentially severe systemic adverse effects such as anaphylaxis [7], a requirement for frequent hospital visits, and pain at the injection site. For these reasons, sublingual immunotherapy (SLIT) has been proposed as an alternative to SCIT. SLIT reduces the burden on patients because the therapy can be administered at home and has fewer severe side effects. The efficacy and safety of SLIT have been shown in double-blind comparative studies in Europe and North America [8-11] and this therapy has become a major alternative to SCIT.

Clinical studies of the efficacy and safety of sublingual immunotherapy (SLIT) for JC pollinosis have been conducted in small patient populations [12-14]. In these studies, standardized JC pollen extract for SCIT was applied in the sublingual cavity and was spit out

after 2 minutes holding. The dosing regimen consisted of an induction phase for 3 to 4 weeks with daily increasing doses 5 to 7 days a week, followed by a maintenance phase with a dose of 2000 Japanese allergy unit (JAU)/mL once weekly for the rest of the study. Horiguchi et al. [12] and Okubo et al. [13] evaluated the efficacy and safety of SLIT for 7 months in one pollen season, while Fujimura et al. [14] used a treatment period of 18 months to cover 2 pollen seasons and observed the carryover effect in the third pollen season without treatment. Horiguchi et al. [12] and Okubo et al. [13] found significant improvement in QOL scores, but effects on symptom scores were inconsistent between the two studies. Treatment for 18 months had efficacy in the second pollen season, and in the third season after treatment was terminated after the second season, but failed to show a significant effect in the first season [14]. None of the studies showed any serious side effects, such as anaphylaxis.

The differences in results among these studies might be due to the limited number of patients, different treatment periods, and variable pollen counts in different seasons. However, despite some inconsistencies, these studies suggest that the sublingual route might be effective for allergen-specific immunotherapy for JC pollinosis. Thus, a formulation (CEDARTOLEN) of standardized JC pollen extract at 200 and 2000 JAU/mL has been developed for this purpose, using a container with a pump that expels 0.2 mL/push for the induction phase at 200 and 2000 JAU/mL, and a single use pouch with 1 mL of 2000 JAU for the maintenance phase. Using this formulation, we conducted a placebo-controlled double-blind randomized clinical trial in 531 patients with JC pollinosis to investigate the long-term efficacy and safety of SLIT using this formulation.

METHODS

Subjects

The subjects were patients with JC pollinosis who met inclusion criteria of male or female, age 12-64 years, JC-specific immunoglobulin E (IgE) levels (ImmunoCAP) of class 3 or higher, and symptoms of JC pollinosis for the previous 2 years; and did not meet exclusion criteria of perennial allergic rhinitis, drug-induced rhinitis, non-allergic rhinitis requiring treatment, previous immunotherapy for JC pollinosis, immunotherapy within the previous 5 years, an asthma attack within the previous 5 years, and pregnancy.

Study drugs

Doses of 200 and 2000 JAU/mL of JC pollen extract were used in the study. The solution of 200 and 2000 JAU/mL were formulated by dilution of standardized Japanese cedar pollen extract original solution 10000 JAU/mL (7.3-21 ug/mL Cry j 1) to give indicated potency, respectively (Torii Pharmaceutical Co. Ltd., Tokyo, Japan). A container with a pump to provide 0.2 mL in one push was used in the induction phase at doses of 200 and 2000 JAU/mL. A single usage pouch for the maintenance phase was used to deliver 1 mL of 2000 JAU/mL. The placebo consisted of 50% glycerine and containing sodium chloride and was similar to the active drug in appearance, taste and smell.

Study design

This phase III multicentre, randomized, double-blind, placebo-controlled, parallel group comparative study was started in October 2010. A total of 531 patients with JC pollinosis were recruited from 12 medical institutions in Tokyo and surrounding areas, where the pollen season and JC pollen count were estimated to be similar. Patients were randomized into a JC pollen extract (SLIT) group and a placebo group in a 1:1 allocation ratio. Treatment was given for an average of 18 months from October 2010 to April 2012. The treatment began 4 months before

the predicted start of the JC pollen season in 2011 and continued to the end of the JC pollen season in 2012. The longest treatment period was 83 weeks. Randomization was performed by CRO (Bell Medical Solutions Inc.). The randomization codes was generated by a trial independent statistician. To prevent leakage of information, randomization codes are kept strictly confidential, accessible only to authorized persons until the time of un-blinding.

Patients were instructed to place the study drug under their tongue and to keep it in their mouth for 2 minutes before swallowing. They were also requested to place nothing in their mouth and not to gargle for 5 minutes after swallowing. The dosing schedule comprised an initial 2-week induction period in which the dose was titrated every day from 40 JAU per day to 2000 JAU/day, followed by a maintenance period at a daily dose of 2000 JAU/day. The dosing schedule is shown in Table 1.

All patients provided written informed consent before inclusion in the study. The study was approved by the institutional review board of each of the 12 participating institutes and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Measurement of the JC pollen count

The airborne pollen count was measured with the Durham method [15] at Chiyoda ward in Tokyo by the public service.

Evaluation of symptoms

Scores were obtained for nasal symptoms, sneeze, rhinorrhoea and nasal congestion using a 5-point scale (0: none, 1: mild, 2: moderate, 3: severe, 4: very severe) based on the Japanese guidelines for allergic rhinitis [6]. Ocular symptoms (eye itchiness and watery eyes) were scored

using a 4-point scale (0: none, 1: mild, 2: moderate, 3: severe).

The periods of evaluation were January 8 to April 30 in 2011 and 2012. Patients were not allowed to use any medicine for prophylaxis or treatment of JC pollinosis in these periods, including antihistamines or systemic or topical steroids. However, for unbearable symptoms (a nasal symptom with a score of 4 or an ocular symptom with a score of 3), a daily dose of the following relief medications was allowed: fexofenadine hydrochloride (60 mg tablet), tramazoline hydrochloride (nasal solution 0.118%), or ketotifen fumarate (ophthalmic solution 0.05%). The use of each relief medication was scored as 0 (not used) or 3 (used) and a total drug score was calculated (range 0–9).

Evaluation was performed in each JC pollen season and in each peak symptom period. The pollen season was defined as starting on the first day of the first two consecutive days after January 1 on which there was a pollen count $\geq 1/cm^2$ per day, and ending on the day before the first day of the first three consecutive days on which there was a pollen count of $0/cm^2$ per day. The peak symptom period was defined as the week with the worst symptoms based on the sum of nasal symptom and medication scores for all subjects, plus the weeks before and after this week. To avoid results being confounded by pollens from Japanese cypress, which scatter after the cedar season, the peak symptom period was completed before March 31. During the peak symptom period, subjects completed the Japanese Allergic Rhinitis QOL Standard Questionnaire (JRQLQ) No.1 for assessment of QOL [16-18].

Outcome measures

The primary endpoint was the total nasal symptom and medication score (TNSMS; range 0-18). This score included the nasal symptom scores for sneeze, rhinorrhorea, and nasal congestion and drug scores for fexofenadine tablets and tramazoline nasal spray during the peak

symptom period in the second season.

The secondary endpoints were the average of nasal and ocular symptom scores and drug scores for nasal and ocular use during the peak symptom period in the first and second JC pollen seasons; and the total ocular symptom and medication score (TOSMS), which included the ocular symptom score (itchiness and watering of eyes) and the drug score for ketotifen ophthalmic solution.

Electronic diary records

Subjects used an electronic diary (Fujitsu Ltd., Tokyo, Japan) to record symptoms (sneeze, rhinorrhoea, nasal congestion, eye itchiness, and watery eyes) and use of relief medications from January 8 to April 30 in 2011 and 2012.

Measurement of serum immunoglobulins

Serum IgE, JC pollen-specific IgE, and JC pollen-specific IgG4 were measured at 7 time points: before initiation of dosing, and before, in the middle and at the end of the pollen seasons in 2011 and 2012. Assays were conducted at Mitsubishi Chemical Medience (Tokyo, Japan).

Safety

Adverse effects were categorized as mild (no impact on activities of daily living (ADL)), moderate (decreased or affected ADL), or severe (inability to perform ADL or death).

Statistical analysis

Based on the results of the clinical study by Fujimura et al. in 2009 [14], the TNSMS during the peak symptom period were assumed to be 5.8 and 6.8 in the SLIT and placebo groups,

respectively, and the standard deviation of the difference between these groups was assumed to be 3.1. Based on these assumptions, the required sample size was 150 subjects in each group with 80% power and two-tailed alpha level of 0.05. However, we anticipated a high number of dropouts because of the prolonged study period, which included continuation of dosing in the season when subjects were asymptomatic. It was also possible that JC pollen counts would be lower in 2012 and that subjects would have milder symptoms. For these reasons, a larger study population was required to provide sufficient power for analysis, and the target sample size was adjusted to 220 subjects per group.

Data analysis was performed by a biostatistician in Torii Pharmaceutical Co. Ltd.. Efficacy analyses were performed on the corresponding modified intent-to-treat analysis set, which was defined as all patients who received at least 1 dose of sublingual JC pollen extract and had at least 50% TNSMS measurements during the peak symptom period for each season.

For the primary endpoint, a t-test was used to compare the average TNSMS during the peak symptom period in the second season between the two groups. For the other endpoints of TNSMS in first season and TOSMS/drug scores/symptom scores in both first and second season are analyzed in the same way as the primary endpoints. Average TNSMS and average TOSMS during the JC pollen season were also analyzed by using a t-test. JRQLQ No.1 was analyzed by a Wilcoxon rank sum test. Descriptive statistics were used for demographic and for adverse events.

Plots of TNSMS and TOSMS by day in both first and second season are presented as the mean value with JC pollen count. Plots of JC pollen-specific IgE and JC pollen-specific IgG4 are presented as the mean value with p-values for changes from baseline and end of 2011 season by using a paired t-test.

RESULTS

Subjects

A total of 630 subjects provided written informed consent. Of these subjects, 99 were lost during the observation period and 531 were included in the study and randomized into the SLIT (n = 266) and placebo (n = 265) groups. A flowchart of the study is shown in Figure 1. The same number of subjects in each group (n = 241) completed the study. The baseline demographic characteristics of the subjects are shown in Table 2. There were no significant differences between the groups.

JC pollen counts and evaluation period

Treatment was started at an average of 4 months before the expected start of the 2011 JC pollen season. The pre-season treatment period ranged from 9 to 20 weeks. In 2011, a large amount of JC pollen was scattered and the total pollen count was 6537 /cm^2. The JC pollen season (89 days) lasted from February 17 to May 16, and the peak symptom period was March 7 to 27. In 2012, the amount of JC pollen was smaller, with a total count of 1256 /cm^2. The JC pollen season (56 days) lasted from March 3 to April 27, and the peak symptom period was March 19 to 31. The mean pollen count in Tokyo in the last 10 years was 3200 /cm^2.

Efficacy of SLIT with JC pollen extract

The mean TNSMS and TOSMS scores in the 2011 and 2012 JC pollen seasons are shown in Figure 2. The primary endpoint (mean TNSMS) was significantly lower in the SLIT group than in the placebo group in the 2012 peak symptom period (4.00 vs. 5.71; $p < 0.0001$). Similarly, the mean TNSMS in the SLIT group was significantly lower than in the placebo group in the other evaluation periods in JC pollen seasons 2011 and 2012 and in the 2011 peak symptom period ($p < 0.0001$) (Table 3). The SLIT group had significantly lower TOSMS, symptom scores and

medication scores than the placebo group for all items in all periods (Table 3). Improvement of each endpoint in the SLIT group compared to the placebo group was greater in the second season. The respective percentages of patients with TNSMS < 4 points during the peak pollen dispersal season in the SLIT and placebo groups were 19.9% and 12.1% in 2011, and 61.0% and 39.4% in 2012 (Table 4). The total QOL score was also significantly ameliorated in the SLIT group at the peak of pollen dispersal in 2012 (Table 5).

Serum immunoglobulins

Serum levels of JC pollen-specific IgE and JC pollen-specific IgG4 are shown in Figure 3. The JC-specific IgE level significantly increased by up to twice the baseline level 2 months after the start of treatment. The elevated level of JC-specific IgE persisted until the end of the first pollen season. This level decreased in the second season, but was still higher than the baseline level at the end of the second season. The serum level of JC-specific IgG4 increased significantly to five times the baseline level after the 2011 JC pollen season. This level gradually decreased over until the end of the second season, but was still higher than the baseline level after the second season. Neither the JC-specific IgE nor JC-specific IgG4 level correlated with the severity of symptoms or efficacy of treatment (data not shown).

The average ratio of JC-specific IgE to total IgE prior to treatment (sIgE/tIgE) was 0.18 in all patients in the study. The SLIT group was divided into subgroups with sIgE/tIgE ratios $\geqq$ 0.18 and < 0.18. Similar subgroups were established in the placebo group. The TNSMS in the 2012 peak pollen season in each low sIgE/tIgE subgroup was significantly lower than that in the respective high sIgE/tIgE subgroup, but with no difference between the SLIT and placebo groups (Figure 4).

Safety

There were 7 serious adverse events in the SLIT group and 6 in the placebo group, with no causal relationship between any of these events and the JC extract or placebo. At least one adverse event occurred in 212 of the 266 subjects (79.7%) in the SLIT group and in 189 of the 265 subjects (71.3%) in the placebo group. Most of the adverse events were mild and required no treatment. No systemic anaphylactic reactions and no deaths occurred during the study. Treatment-related adverse events occurred in 36 subjects (13.5%) in the SLIT group and 14 (5.3%) in the placebo group (Table 6). In the SLIT group, the most common treatment-related adverse event was oedema mouth (10 subjects), followed by stomatitis, throat irritation, headache, oral pruritus and ear pruritus (Table 7). oedema mouth did not occur in the placebo group. The treatment-related adverse events were mild (n = 49) or moderate (n = 3). None were severe. Adverse effects (except for severe adverse effects) leading to discontinuation of the study occurred in 4 subjects in the SLIT group and one in the placebo group. Of these, toxic eruption in one subject in the SLIT group was identified as a treatment-related adverse event.

Discussion

This is the first large randomized multicentre placebo-controlled double-blind parallel group study of the efficacy and safety of SLIT using a new formulation of standardized JC pollen extract for JC pollinosis in Japan. The primary endpoint, TNSMS in the peak symptom period in the second season (2012), was significantly improved by 30% in the SLIT group compared with the placebo group, and all secondary endpoints, including TOSMS, were also significantly improved. The dosing regimen included a daily dose of 2000 JAU/mL in the maintenance period after induction, compared to the weekly dose given in this period in previous studies [12-14]. This may underlie the greater improvements in TNSMS, TOSMS, and symptom and

medication scores in this study compared to the previous studies.

Evaluation of the efficacy of treatment for pollinosis is difficult because the amount of scattered pollen and climatic conditions vary from year to year. In this study, the airborne pollen counts were 6537 /cm^2 in 2011 and 1256 /cm^2 in 2012, while those in earlier studies were 10625 /cm^2 in 2005 [13], 1154 /cm^2 in 2006 [12], 2777 /cm^2 in 2007 [14], 6596 /cm^2 in 2008 [14], and 5486 /cm^2 in 2009 [10]. Based on these data, the airborne pollen counts in this study were within the range of counts in the earlier studies. The pollen count in the first season of this study was higher than that in the first season in Fujimura et al. [10], but significant improvements in symptom and medication scores in this season were found in the current study, but not in Fujimura et al. [14]. The response in this study might be due to use of a daily dose of 2000 JAU/mL in the maintenance period, compared to the weekly dose in Fujimura et al. [14]. This suggests that daily dosing may improve the immunological response.

Treatment commenced at an average of 4 months before the expected start of JC pollen scattering. Large-scale scattering occurred in the first season, but the SLIT group showed significant improvements in all evaluated items, compared with those in the placebo group. A large clinical study of grass pollen tablets in Europe [19] and in North America [20] showed the efficacy of treatment started 4 months in advance of the grass pollen season. Similarly, SLIT with JC pollen extract from 4 months pre-season was effective in the first season. We note that TNSMS in the SLIT group showed a greater improvement in the second season than the first season. The different JC pollen counts in the two seasons make it difficult to compare treatment scores with certainty and many of the patients in this study were not treated for four months

prior to pollen dispersal in the first season. Recent studies have compared pre-coseasonal, coseasonal and continuous administration of sublingual immunotherapy [21,22] however, it is difficult to conclude that continuous treatment over multiple seasons provide better efficacy.

Most side effects in the current study were mild and were related to the site of administration (oedema mouth, stomatitis and throat irritation). This is also consistent with previous SLIT trials [12-14]. Thus, SLIT with JC pollen extract has an excellent tolerance profile and may be a new treatment of choice for JC pollinosis.

In a large clinical study using sublingual grass pollen tablets [23,], the optimal dose of the major allergen was found to be 600 μg/month. The maintenance dose used in this study was 2000 JAU daily, which results in delivery of the major allergens (Cry j 1 and Cry j 2) at doses of 90-150 μg/month. At a concentration higher than 2.000 JAU/ml, it is difficult to maintain the stability of the cedar pollen liquid extract at 2~8°C, which is important for ensuring the distribution of the products. Despite this dose being less than the optimal major allergen dose for grass pollen tablets, the dose of JC pollen extract improved TNSMS in the second season by 30%, comparable to the efficacy in the clinical study of sublingual grass pollen tablets [24]. Thus, the amount of allergen required to treat JC pollinosis was less than that expected from other studies and less than the recommended amount for immunotherapy by the World Allergy Organization (WAO). This suggests that JC pollinosis may be a unique case or that a higher dose of JC pollen

extract might give better efficacy. However, it was technically difficult to prepare a solution with a higher concentration of allergen because of the unstable antigenicity of Cry j 1 and Cry j 2. However, a cedar pollen tablet with a higher concentration of cedar allergen has recently been developed and a clinical study to clarify the dose-response relationship is being planned.

Changes in serum immunoglobulins were monitored throughout the study. JC-specific IgE in the placebo group increased after exposure to pollen in the first season, but not in the second season. This may be because the pollen count in the 2011 season was 5 times higher than that in 2012. JC-specific IgE increased in the SLIT group before the pollen season, which indicated that the immunotherapy itself affected the Th2-mediated response. The increased IgE levels gradually moved back toward baseline at the end of the 18-month treatment period. Previous studies have found no changes in serum JC-specific IgE. The serum JC-specific IgG4 level gradually increased after initiation of SLIT, reached a peak at the end of the first season, and remained at higher levels throughout the study. In contrast, there was no significant change in serum JC-specific IgG4 in the placebo group. The exact mechanisms underlying immunotherapy are unclear, but a rebalancing of Th1 and Th2 responses and an increase in IgG4 are among the possible mechanisms. The changes in serum JC-specific IgE and IgG4 in this study may reflect an altered immune response to JC pollen induced by SLIT. The sIgE/tIgE ratio prior to SLIT has been found to be significantly higher [25] or lower [14] in responders compared to non-responders. In this study, this ratio was significantly lower in responders in the SLIT group, but was also lower in the placebo group in subjects with mild symptoms. Thus, a low sIgE/tIgE ratio prior to the pollen season may be a predictor of mild symptoms in the pollen dispersal season.

The World Health Organization (WHO) [26,27] recommends a treatment period of 3-5 years

for allergen-specific immunotherapy. SLIT using grass pollen tablets has been found to have a disease-modifying effect at 2-year follow-up after 3 years of treatment [28]. Further data from long-term studies of more than 3 years are required to establish the long-term efficacy and disease-modifying effects of SLIT with JC pollen extract.

Conclusion

In this 2-year randomized placebo-controlled double-blind study, SLIT with JC pollen extract was effective in the first and second JC pollen seasons and was well tolerated.

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Disclosures

Dr Y. Okamoto and Dr K. Okubo were the controllers of the study and equally contributed to this study. Dr A. Konno was the medical advisor.

Figure legends

Figure 1: Figure 1: Flow chart of the study using SLIT with JC pollen extract.

A total of 630 subjects provided written informed consent. Of these subjects, 99 were lost during the observation period and 531 were included in the study and randomised into the SLIT (n = 266) and placebo (n = 265) groups. The same number of subjects in each group (n = 241) completed the study.

[a] Drop-out during observation period: 13 subject requests; 51 unmet inclusion criteria; 35 met exclusion criteria.

[b] Discontinuation in first season. *Test-drug group*: 1 subject request (deterioration of disease); 1 subject request (occurrence of adverse effects); 2 personal reasons. *Placebo group*; 1 subject request (deterioration of disease); 6 personal reasons; 1 inappropriate subject; 1 other reason.

[c] Discontinuation in second season. *Test-drug group*: 2 adverse effects; 0 subject requests (deterioration of disease); 1 subject request (occurrence of adverse effects); 8 personal reasons; 5 inappropriate subjects; 2 other reasons. *Placebo group*: 3 subject request (occurrence of adverse effects); 8 personal reasons; 2 inappropriate subjects; 2 other reasons.

Figure 2: Total nasal symptom medication score (TNSMS) and total ocular symptom medication score (TOSMS) in 2011 and 2012

A:TNSMS (2011), B:TNSMS (2012), C:TOSMS (2011), D:TOSMS (2012)

Placebo group [···], SLIT group [－], JC pollen count [▒]).

Figure 3: Serum levels of JC pollen specific IgE (A) and IgG4 (B).

A: JC pollen specific IgE, B:JC pollen specific IgG4

Placebo group [···], SLIT group [－], JC pollen scattering period [▒]).

Figure 4: Relationship of TNSMS in 2012 with the specific IgE/total IgE ratio prior to treatment in the SLIT and placebo groups.

A: JC pollen extract, B: Placebo