Japanese cedar pollen sublingual immunotherapy is effective in treating seasonal allergic rhinitis during the pollen dispersal period for Japanese cedar and Japanese cypress

Dear Editor,

In Japan, allergic rhinitis is one of the most prevalent allergic diseases, and there has been an increase in seasonal allergic rhinitis in recent years. Matsubara et al. reported that the overall prevalence of allergic rhinitis was 49.2%, with a marked increase in Japanese cedar (JC) pollinosis among teenagers. Over the past 20 years, the prevalence of JC pollinosis increased from 16.2% in 1998 to 26.5% in 2008 and 38.8% in 2019, and that of non-JC pollinosis also increased from 10.9% to 15.4% and 25.1%, respectively. It is assumed that this may reflect an increase in Japanese cypress (JCY) pollinosis, in addition to increases in grass pollinosis and Asteraceae pollinosis.3

JC pollinosis is a typical type I allergic disease in which nasal, ocular, pharyngeal, and skin symptoms occur during the JC pollen dispersal season. JC pollinosis significantly affects daily activity, work productivity, learning, sleep, and quality of life. Furthermore, approximately 70% of patients with JC pollinosis are also allergic to JCY pollen.1 It has been reported that almost all cases positive for specific immunoglobulin E (sIgE) antibody against JCY (JCY-sIgE) also have sIgE antibody against JC (JC-sIgE), and patients who are positive for only JCY-sIgE, i.e., negative for JC-sIgE, are rare.4 Recently, seasonal allergic rhinitis with JCY pollen dispersal has attracted attention, and its clinical relevance to JC pollinosis has been described. Because of the overlap of the dispersal period of JC pollen and that of JCY pollen, patients with combined JC and JCY pollinosis experience severe symptoms from February to April, when cedar pollen is dispersed, as well as from April to May, when cypress pollen is dispersed. Therefore, it is important to control their symptoms during this long period.

JC pollen sublingual immunotherapy (SLIT) tablets are available for use against JC pollinosis in Japan. These tablets are fast-dissolving, freeze-dried tablets containing JC pollen allergen extracts, including the major allergens, Cry j 1 and Cry j 2; these two allergens have strong amino acid sequence homology with the major allergens of JCY pollen, Cha o 1 and Cha o 2, respectively.5 In the field of marketing authorization for industrially manufactured allergen products in Europe, the concept of homologous groups has been introduced by the European Medical Agency. According to this concept, the data of one allergen extract demonstrating stability, efficacy, and safety can, to a limited extent, be extrapolated to other allergen extracts belonging to the same homologous groups.6 Cedar and cypress are homologous groups of tree species within the family Cupressaceae. However, the clinical efficacy of JC pollen SLIT tablets for allergic symptoms with JCY pollen dispersal has been controversial in actual clinical settings. Here, we report the efficacy of JC pollen SLIT tablets against seasonal allergic rhinitis during the JC pollen and JCY pollen dispersal periods from a phase II/III study (JapicCTI no. 142579).

This randomized, double-blinded, placebo-controlled phase II/III trial was conducted to investigate the optimal dose of JC pollen SLIT tablets and examine the long-term efficacy and safety over 3 years with the selected dose and during a 2-year follow-up. We have already reported the beneficial sustained efficacy of JC pollen SLIT tablets in a treatment duration-dependent manner when using the total nasal symptom and medication score (TNSMS) during the peak symptom period for JC pollen as the primary endpoint. Here, we show the TNSMS of patients who consumed placebo SLIT tablets (Placebo group, n = 159) or SLIT tablets containing 5000 Japanese allergy units (JAU) of JC pollen (5000 JAU group, n = 158) for 3 years. The daily average TNSMS in the 500 JAU group was lower than that in the Placebo group during the JC pollen and JCY pollen dispersal period in all three seasons (Fig. 1A). Notably, the degree of increase in TNSMS in the 5000 JAU group was lower than that in the Placebo group in the third season, especially as the JCY pollen dispersed increasingly more (JCY pollen had a higher peak value compared with JC pollen) (Fig. 1A, third season). A relative reduction in TNSMS compared with the Placebo group was seen in the 5000 JAU group in a treatment duration-dependent manner (first, second, and third seasons: 28.6%, 40.2%, and 42.8% vs Placebo, respectively; p < 0.001, Fig. 1B). The total ocular symptom and medication score (TOSMS), examined as a secondary endpoint, also showed similar beneficial outcomes in the 5000 JAU group compared with the Placebo group (Fig. 2). These results suggest that JC pollen SLIT tablets sustained a clinically relevant effect against seasonal allergic rhinitis during not only the JC pollen dispersal period but also the JCY pollen dispersal period. Furthermore, the 5000 JAU group had significantly reduced TNSMS with clinically relevant effects compared with Placebo group even when evaluated separately for the JC pollen dispersal period and the JCY pollen dispersal period which was tentatively defined as after the day the JCY pollen count exceeded 30 grains/
cm²/day, a greater impact on symptoms caused by JCY pollen than JC pollen, because of the overlap between the JC pollen and JCY pollen dispersal periods (Supplementary Table 1).

Recently, a new major allergen of JCY pollen, Cha o 3, was discovered, and it has strong amino acid sequence homology with the major allergen of JC pollen, Cry j 4. Osada et al. reported that a low amount of Cry j 4 is included in JC pollen allergen extracts. However, the extent to which Cha o 1, Cha o 2, and Cha o 3 each contribute to the clinical symptoms with JCY pollen dispersal are not fully understood. In the present study, approximately 80% of the patients in both the Placebo and 5000 JAU groups were positive (≥0.7 kUA/L) for JCY-sIgE antibodies at baseline (Supplementary Table 2), but the presence or absence of historical clinical symptoms to JCY pollen in each subject was not confirmed. However, even when JCY-sIgE positive patients alone were analyzed, the relative reductions in TNSMS and TOSMS in the 5000 JAU group were significantly lower than for Placebo group during the JC pollen and JCY pollen dispersal periods over three seasons. In addition, similar results were observed when JCY-sIgE pseudo-positive (≥0.35 kUA/L) patients were included (Supplementary Fig. 1). The remaining approximately 20%
of patients who were negative (<0.7 kUa/L) for JCY-sIgE in the Placebo group also increased both their TNSMS and TOSMS in a manner similar to that of Placebo group subjects positive for JCY-sIgE, depending on the JCY pollen dispersal throughout the study, while the score of TOSMS were generally low in the subjects who were negative for JCY-sIgE. It is presumed that JC pollinosis patients who are negative for JCY-sIgE are immunologically affected by JCY pollen because of the common allergen between JC pollen and JCY pollen. This suggests that it is important to handle allergic symptoms caused by JC pollen and JCY pollen not separately but comprehensively as cedar-cypress combined pollinosis.

This phase II/III study was conducted in the Tokyo metropolitan area. Because the area of cypress plantations is larger in western Japan, the amount of JCY pollen dispersed in western Japan was...
estimated to be larger than that in eastern Japan, including Tokyo. However, over the past 10 years (2009–2018), including the present evaluation period, the amount of JCY pollen dispersed in the Tokyo metropolitan area was equal to or greater than that in western Japan. The ratio of JCY pollen to the total dispersal amount of JC pollen and JCY pollen was higher in western Japan (approximately 50%) than that in the Tokyo metropolitan area (20–30%); therefore, in addition to the clinical relevance of the ratio of JCY pollen, the impact of the JCY pollen dispersal pattern, large amounts over several days, will be anticipated in the future. Here, we found that JC pollen SLIT tablets were effective at treating seasonal allergic rhinitis during the pollen dispersal period for Japanese cedar and Japanese cypress, as well as in the individual JC pollen and JCY pollen dispersal periods. Thus, we will examine the efficacy of JC pollen SLIT tablets in patients with clinical symptoms triggered by JCY pollen to further determine the usefulness of JC pollen SLIT tablets for treating combined JC and JCY pollinosis, which is the same homologous group.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2021.08.012.

Conflict of interest

MG has received honoraria from Taiho, Hisamitsu, Meiji Seika Pharma, and Novartis. KO has received a consultancy fee, honoraria, writing fee, and scholarship donation from Torii. YO has received a consultancy fee and honoraria from Torii. YM is an employee of Torii. SY, MO, and TK have no conflict of interest.

Syuji Yonekura a, Minoru Gotoh b, Mitsuhiro Okano c, Tomoya Kurokawa a,d, Yuriko Maekawa e, Kimihiro Okubo f, Yoshitaka Okamoto f

a Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
b Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
c Department of Otitismedia, International University of Health and Welfare, Chiba, Japan
d Clinical Research Center, Chiba University Hospital, Chiba, Japan
e Department of Medical Affairs, Torii Pharmaceutical Co., Ltd., Tokyo, Japan
f Chiba Rosai Hospital, Chiba, Japan

corresponding author. Medical Affairs Department, Torii Pharmaceutical Co., Ltd., 3–4–1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan.
E-mail address: yuriko.maekawa@torii.co.jp (Y. Maekawa).

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