Real-world efficacy of sublingual immunotherapy with Japanese cedar pollen for cypress pollinosis

Aiko Oka, MD,[a] Tamami Yamashita, MD,[b] Kengo Kanai, MD,[a,c] Atsushi Yuta, MD,[d] Yukiko Ogawa, MD,[d] Eriko Takahara, MD,[e] Hideki Shiratsuchi, MD,[f] Akihiko Terada, MD,[g] Takatsugu Tsunoda, MD,[h] Takeshi Masuda, MD,[i] Satoru Masuno, MD,[j] Kenichi Kanai, MD,[k] Hitoshi Nagakura, MD,[l] Reiko Tokuda, MD,[m] Harumi Arao, MD,[n] Hitoshi Bamba, MD,[o] Shigenobu Yasuda, MD,[p] Hideya Mimura, MD,[q] Mahoko Nakazato, MD,[r] Hidehisa Nakazato, MD,[s] Noriyuki Houya, MD,[t] Hideaki Tsuzuki, MD,[u] Masaharu Tokuriki, MD,[v] Mayuko Sakaida, MD,[w] Ryo Amesara, MD,[x] Chikahisa Ohkawa, MD,[y] Takemitsu Hama, MD,[z] Hiroki Ikeda, MD,[aa] Hisaki Fukushima, MD,[bb] Sumiko Niitsu, MD,[cc] Hirofumi Sakaguchi, MD,[dd] Norihito Iba, MD,[ee] Hiroshi Kumanomidou, MD,[ff] Yoshiyuki Hyo, MD,[gg] Ryo Takagi, MD,[a] Takashi Koike, MD,[a] Marie Yamada, MD,[a] and Mitsuhiro Okano, MD[a]

Chiba, Hyogo, Mie, Tokyo, Fukuoka, Aichi, Saitama, Kanagawa, Shiga, Kyoto, Wakayama, and Okayama, Japan

Background: It remains unclear whether allergen immunotherapy with Japanese cedar pollen extract is effective for Japanese cypress pollinosis in real-world settings.

Objective: We sought to investigate the Japan-wide prevalence of cypress pollinosis, the efficacy of cedar sublingual immunotherapy (SLIT) on cypress pollinosis, the role of serum-specific IgE levels in pollinosis, and patients' interest in the development of cypress SLIT.

Methods: A cross-sectional, multicenter study using self-administered questionnaires was conducted in regions of Japan where cedar and cypress pollen dispersals are prevalent. This study included patients aged 5 to 69 years who received cedar SLIT in 2023.

Results: Of 2597 participants analyzed, 84.5% experienced pollinosis symptoms during the cypress season before receiving cedar SLIT. Among these patients, 40.2% felt that cedar SLIT was less effective during the cypress season than during the cedar season. The longer the patients received cedar SLIT, the greater the inefficacy perceived during the cypress versus the cedar season. In the symptomatic patients, serum IgE levels were significantly higher for cedar and cypress as compared with those observed in subjects without symptoms during the cypress season. No significant differences were reported in IgE levels for cedar and cypress between patients reporting either high or lower efficacy for the cedar SLIT during cypress season. Interest in cypress SLIT was seen in 78.4% of these patients.

Conclusions: Although there is a bias based on regional distribution, cedar SLIT has induced a limited efficacy on cypress pollinosis in real-world settings, suggesting a need for the development of cypress SLIT. (J Allergy Clin Immunol Global 2025;4:100463.)

Key words: *Efficacy, IgE, Japanese cedar pollen, Japanese cypress pollen, pollinosis, prevalence, real-world evidence, sublingual immunotherapy*

Allergic rhinitis (AR) has become one of the major allergic diseases that can cause huge socioeconomic burden.[1-4] The prevalence of AR has been reported to be 19% to 32% in Europe, 15% in the United States, and 27% to 49% in Asia.[5-8] Cedar and cypress trees were popular building materials for traditional Japanese houses and were planted nationwide after World War II. However, over time they have become less used, and, unfortunately, the pollen of these cedar and cypress trees are responsible for spring seasonal AR that occurs in 38.8% of the Japanese population.[4] Allergen immunotherapy (AIT) was developed and has been used since 1911, when Noon[9] reported on the efficacy of the first grass pollen subcutaneous immunotherapy (SCIT). Passalacqua et al[10] published the first report that provided details on the efficacy of sublingual immunotherapy (SLIT), which can be used as an alternative to SCIT because of its safety and convenience.[10] Cedar pollen SLIT became available in 2014 in Japan and has shown not only clinical but also economic efficacy in patients with cedar pollinosis.[11-13] Both SLIT and SCIT using Japanese cedar pollen extract are available in Japan, and both treatments are effective.[14,15] However, SCIT is currently not popular in Japan because of injection-related pain, a higher risk of

From [a]the Department of Otorhinolaryngology and [b]the Faculty of Medicine, International University of Health and Welfare School of Medicine, Chiba; [c]the Department of Otorhinolaryngology, Head and Neck Surgery, Japanese Red Cross Society Himeji Hospital, Hyogo; [d]Yuta Clinic, Mie; [e]Chofu Ekimae ENT Clinic, Tokyo; [f]Shiratsuchi Otorhinolaryngology Clinic, Fukuoka; [g]Terada Allergy Kodomo Clinic, Aichi; [h]Hidamari Clinic, Mie; [i]Masuda ENT Clinic, Saitama; [j]Makinohara Nanohana ENT Clinic, Chiba; [k]Kosugi ENT Clinic, Kanagawa; [l]Nagakura ENT Allergy Clinic, Tokyo; [m]Tokuda Family Clinic, Mie; [n]Arao Internal Medicine and Otolaryngology Clinic, Aichi; [o]Bamba ENT Clinic, Shiga; [p]Yasuda Clinic, Kyoto; [q]Mimura Clinic, Aichi; [r]Azusawa ENT Clinic, [s]Oyamanakamaru Clinic, and [t]Oizumigakuen ENT Clinic, Tokyo; [u]Miyako Ear, Nose and Throat Clinic, Aichi; [v]Tokuriki ENT Clinic, [w]Mie ENT Clinic, [x]Amesara ENT Clinic, and [y]Ohkawa ENT Clinic, Mie; [z]Hama ENT Clinic, Kyoto; [aa]Ikeda ENT Clinic, Wakayama; [bb]Fukushima Clinic and [cc]Niitsu Clinic, Okayama; [dd]E.N.T. Sakaguchi Clinic, Shiga; [ee]Minna-no-kodomo Allergy Clinic, Wakayama; [ff]Kumanomidou ENT Clinic, Tokyo, Japan; and [gg]Hyo ENT Clinic, Kyoto.

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Corresponding author: Mitsuhiro Okano, MD, Department of Otorhinolaryngology, Head & Neck Surgery, International University of Health and Welfare Narita Hospital, 852 Hatakeda, Narita 286-8520, Japan. E-mail: mokano@iuhw.ac.jp.

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Abbreviations used
AIT: Allergen immunotherapy
AR: Allergic rhinitis
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy

systemic adverse events including anaphylaxis, and frequent hospital visits. The confidential data (not shown) indicate that yearly shipment of cedar SCIT extract has not changed, whereas the shipment of cedar SLIT tablets has dramatically increased since the product was launched on the market. In contrast, as compared with cedar pollinosis, cypress pollinosis has not received as much attention, even though in Japan the prevalence of cypress sensitization is the second highest after cedar.[16] Furthermore, the efficacy of cedar SLIT on cypress pollinosis remains unclear and there have been variable results.[17-19] For example, a *post hoc* analysis using a randomized, double-blind, placebo-controlled trial of cedar SLIT for patients with cedar pollinosis that was performed in Tokyo, Japan, showed that cedar SLIT effectively suppressed the symptoms during the cypress season.[19] In contrast, our recent multicenter clinical survey demonstrated that 37.4% of patients with cypress pollinosis experienced a decreased efficacy of cedar SLIT because of the presence of cypress pollen during the cypress season, with this decreased efficacy also found to exhibit regional differences throughout Japan.[20] Cedar SLIT induces IL-10 production in peripheral blood.[21] IL-10 is a regulatory cytokine that has been reported to be associated with the efficacy of SLIT by PBMCs released *in vitro* in response to Cry j 1, which is the major allergen component of cedar pollen.[21] However, this production was not induced by Cha o 1 or Cha o 3, which are the major allergen components of cypress pollen, and there were similar results seen in the serum-specific IgG4 levels.[21] Cedar SLIT increased cedar pollen–specific IgG4,[21-23] whereas total IgG4 was not elevated in high responders after cedar SLIT.[24]

Because most of the patients with AR are polysensitized, this can make treatment with AIT difficult for these patients.[25-27] The possible allergens that cause rhinitis symptoms during post–cedar pollen season are not only cypress pollen but also grass and birch pollen and house dust mites. Detection of the allergens associated with the rhinitis symptoms is critical for the administration of a successful AR treatment, especially in AIT.

The objective of our present study was to investigate the prevalence of cypress pollinosis, the efficacy of cedar SLIT on cypress pollinosis, the role of serum-specific IgE levels in cypress pollinosis, the efficacy of cedar SLIT during cypress season, and the patients' interest in the potential development of cypress SLIT.

METHODS

Subjects

This cross-sectional, multicenter study used a self-administered questionnaire that covered large areas in Japan where both cedar and cypress pollen are dispersed. Patients who had started receiving cedar SLIT before the cedar season in 2023 and were aged between 5 and 69 years were eligible for this study. The protocol of SLIT approved in Japan involves continuous therapy, whereas preseasonal and coseasonal therapies are not approved. Thus, all the subjects received year-round SLIT. Written informed consent was obtained from the patients or guardians. Patients, including 5-year-old patients, who needed support to fill out the questionnaire were supported by their guardians. Immunocompromised patients were excluded. All the subjects started SLIT with a 2000 Japanese allergy unit (JAU) cedar tablet for 1 week followed by a 5000 JAU tablet every day as a maintenance dose. For patients who experienced adverse reactions, clinicians attempted dose reduction, abbreviated sublingual retention, or cessation of immunotherapy. Notably, those who ceased immunotherapy were not included in this study. Although we did not collect the data on dose reduction including shortened sublingual retention, a coauthor of this study reported that the rate of patients who needed dose reduction in cedar SLIT was 2.5%.[28] This study was conducted as part of a research (titled "Development of allergen immunotherapy for Japanese cedar and cypress pollinosis targeting no severe condition") funded by the Japan Agency for Medical Research and Development. The research committee nominated 37 facilities dedicated to SLIT. Thus, the patients reflected a select group referred to these clinics. Between April and May 2023, questionnaires were sent to the 37 facilities, with the survey conducted after the peak cypress pollen dispersal season mainly during June to July. A total of 2626 questionnaires were collected from the following 31 facilities: (1) Amesara ENT Clinic (Mie Prefecture), (2) Arao Internal Medicine and Otolaryngology Clinic (Aichi Prefecture), (3) Azusawa ENT Clinic (Tokyo Prefecture), (4) Bamba ENT Clinic (Shiga Prefecture), (5) Chofu Ekimae ENT Clinic (Tokyo Prefecture), (6) Fukushima Clinic (Okayama Prefecture), (7) Hama ENT Clinic (Kyoto Prefecture), (8) Hidamari Clinic (Mie Prefecture), (9) Hyo ENT Clinic (Kyoto Prefecture), (10) Ikeda ENT Clinic (Wakayama Prefecture), (11) Kumanomidou ENT Clinic (Tokyo Prefecture), (12) Kosugi ENT Clinic (Kanagawa Prefecture), (13) Masuda ENT Clinic (Saitama Prefecture), (14) Minna-no-kodomo Allergy Clinic (Wakayama Prefecture), (15) Makinohara Nanohana ENT Clinic (Chiba Prefecture), (16) Mie ENT Clinic (Mie Prefecture), (17) Mimura Clinic (Aichi Prefecture), (18) Miyako Clinic (Aichi Prefecture), (19) Nagakura ENT Allergy Clinic (Tokyo Prefecture), (20) Niitsu Clinic (Okayama Prefecture), (21) Oizumigakuen ENT Clinic (Tokyo Prefecture), (22) Okawa ENT Clinic (Mie Prefecture), (23) Oyama Nakamaru Clinic (Tokyo Prefecture), (24) Sakaguchi ENT Clinic (Shiga Prefecture), (25) Shiratsuchi ENT Clinic (Fukuoka Prefecture), (26) Tokuda Family Clinic (Mie Prefecture), (27) Tokuriki ENT Clinic (Mie Prefecture), (28) Terada Allergy Kodomo Clinic (Aichi Prefecture), (29) Yasuda Clinic (Kyoto Prefecture), (30) Yuta Clinic (Mie Prefecture), and (31) International University of Health and Welfare Narita Hospital (Chiba Prefecture). The facilities that participated in this study are located in areas where both cedar and cypress pollen are dispersed. There were 15 cases that were excluded because of the lack of answers to the question that asked whether the patient had pollinosis symptoms during the cypress season, and there were 14 cases that were excluded because of age (<5 years or >70 years). After these exclusions, there were 2597 cases that were included in the analysis for this study. Even though we recruited patients from eastern (n = 1611) and western (n = 986) Japan, the distribution of the collaboration facilities was still biased. It has been previously shown that the prevalence of cypress pollinosis and lessened efficacy of cedar SLIT on cypress pollinosis exhibit a regional difference in Japan,[20] which is compatible with the higher level of cypress pollen dispersal

in the western area compared with the eastern area in Japan.[29] The Ethics Committee of the International University of Health and Welfare approved this research and the study protocol (approval no. 21-Nr-091).

Survey content

The questionnaire consisted of 5 questions (Q1-Q5) with multiple choices. We defined the cedar season as lasting from February to mid-March and the cypress season from late March to April. Q1 asked the participants whether they had exhibited any pollinosis symptoms during the cypress pollen season before starting the cedar SLIT, with the answer selected from 3 choices: "yes," "no," and "do not remember." If patients confirmed that they had symptoms during the cypress pollen season and answered "yes" in Q1, they were then subsequently asked to answer the following questions. Q2 asked about the efficacy of the cedar SLIT during the season when the cedar pollen was dispersed in 2023 as compared with that in 2022, with the answer selected from 5 possible choices: "strong," "relatively strong," "similar," "relatively weak," and "weak." Q3 asked about the efficacy of the cedar SLIT during the season when the cypress pollen was dispersed in 2023 as compared with that in 2022, with the answer selected from the same choices presented for Q2. Q4 asked about the efficacy of the cedar SLIT on the symptoms that were present during the cypress pollen dispersal season as compared with that for the cedar pollen dispersal season in 2023, with the answer selected from 5 possible choices: "more effective," "relatively effective," "similar," "relatively ineffective," and "ineffective." Q5 asked about the patient's intent to use cypress SLIT if this were to be developed, with the answer selected from 6 possible choices: "unwilling to receive," "relatively unwilling to receive," "relatively willing to receive," "willing to receive," "no interest," or "other." "Unwilling" indicates that the participants do not want to receive cypress SLIT. "No interest" indicates that they are not interested in cypress SLIT, and we expect that they will not receive it.

Information collected regarding patient background included age and sex, along with information on the following items that were collected and listed by the medical institution: duration of SLIT (how many seasons after the start of SLIT); serum IgE specific for cedar, cypress, grass, birch, and dust mite antigens; and use of medication for rhinoconjunctivitis including oral antihistamines, intranasal steroids, antileukotrienes, ophthalmic antihistamines, dust mite SLIT, and others, such as intranasal vasoconstrictors (n = 19), oral corticosteroids (n = 12), ophthalmic corticosteroids (n = 2), cutaneous antihistamine patches (n = 3), expectorants (n = 3), Chinese medicines (n = 8), and omalizumab (n = 2). The antigen-specific IgE measurement methods used included ImmunoCAP (Thermo Fisher Scientific, Tokyo, Japan), Mast Immunosystems (Resonac Corp, Tokyo, Japan), and View Allergy 39 (Thermo Fisher Scientific).

Statistical analysis

All values are presented as the mean. The parametric Student *t* test was used to compare the data between the groups, and a chi-square test was used for comparisons of the frequencies among the groups. The Pearson correlation coefficient was used for quantifying linear relationships between the specific IgE values. Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, Boston, Mass). *P* values less than .05 were considered statistically significant.

RESULTS

Study population

The total number of participants evaluated was 2597, of whom 1354 (52.1%) were male and 1218 (46.9%) were female, with 25 (1%) for whom sex was not recorded. Fig 1, *A*, presents the age distribution and shows that the largest age group was between 10 and 19 years, with a mean age of 26 years. Fig 1, *B*, presents the duration of the cedar SLIT, with 76.8% (n = 1995) of the participants having continued the treatment for 1 to 3 years. The number of patients who received dual cedar and dust mite SLIT was 789 (38.1% of the 2073 patients who answered the question). Nobody received other SLIT therapies.

Questionnaire answers

Presence of pollinosis symptoms during the cypress dispersal season. For Q1, 2195 patients (84.5%) who had received cedar SLIT confirmed having rhinitis symptoms during cypress pollen season (Fig 1, *C*). The proportion of patients who had pollinosis symptoms during cypress season and required any of the medications was higher than the proportion of patients without any symptoms ($P < .001$; Fig 1, *D*). Notably, 10% to 30% of the patients with cedar SLIT did not take any medication for rhinoconjunctivitis and the proportion of patients without medication increased with the duration of SLIT (see Fig E1, *A*, in this article's Online Repository at www.jaci-global.org).

Self-reported efficacy of cedar SLIT during the cedar and cypress pollen seasons. Patients who had pollinosis symptoms during the cypress season (n = 2195) were further asked to answer questions regarding the efficacy of SLIT. Both cedar and cypress pollen were substantially dispersed in 2023 as well as in 2022 in many areas of Japan[30] (see Table E1 in this article's Online Repository at www.jaci-global.org). For Q2, 52% of the patients felt that the cedar SLIT was more effective (strong + relatively strong) for the pollinosis symptoms during the 2023 cedar season as compared with the 2022 cedar season (Fig 2, *A*). In contrast, for Q3, 35.4% of the patients felt that the cedar SLIT was more effective for the pollinosis symptoms during the 2023 cypress season as compared with the 2022 cypress season (Fig 2, *B*), which indicated that there was a smaller yearly improvement during the cypress versus the cedar season ($P < .001$ by chi-square test). For Q4, 40.2% of the patients felt that the cedar SLIT was less effective (relatively ineffective + ineffective) during the cypress versus the cedar season in 2023 (Fig 2, *C*). Finally, 78.4% (willing to receive + relatively willing to receive) of these patients indicated that they would be open to taking the cypress SLIT if it were indeed developed (Fig 2, *D*). Other answers included "I would like to receive cypress SLIT if it is effective," "I would like to decide after completing cedar SLIT," "If the symptoms worsen, I would like to receive it," and many more.

Effect of the duration of SLIT on yearly improvement

During the first year of the use of the cedar SLIT, 60% of the patients confirmed the efficacy (strong + relatively strong) of the

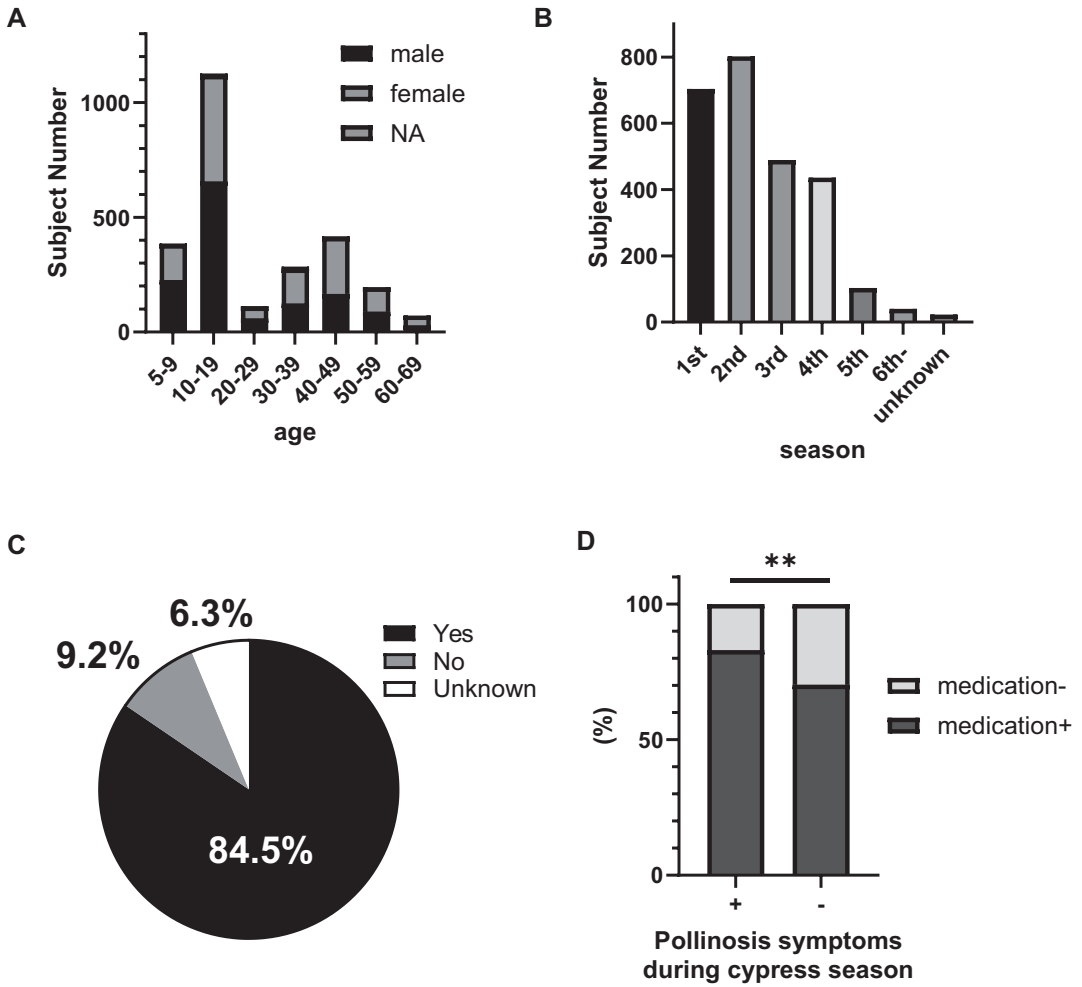

FIG 1. Study population. **A,** Age and sex distribution. **B,** Duration of cedar SLIT. The x-axis represents the season after the initiation of the cedar SLIT. **C,** Proportion of patients with (Yes) and without (No) pollinosis symptoms during the cypress season (Q1). **D,** Comparison of the proportion of patients requiring medications between those with and without pollinosis symptoms during the cypress season. The "+" on the x-axis indicates patients with pollinosis symptoms during the cypress season, and the "−" indicates patients without pollinosis symptoms during the cypress season. *NA,* Not applicable.

cedar SLIT for pollinosis symptoms during the cedar season (Fig 3, *A*). In contrast, 46.4% of the patients confirmed the efficacy of the treatment during the cypress season for the first year of the cedar SLIT use (Fig 3, *B*). However, there was a decrease in the ratio of the patients who felt there was a yearly improvement as compared with the previous season ($P < .001$ for both the cedar and cypress seasons) with more than 70% of the patients in the sixth year or more of treatment who did not feel there was any yearly improvement for either the cedar or the cypress season (Fig 3, *A* and *B*). In addition, the longer the patients received the cedar SLIT, the greater the number of these patients who did not feel there was any efficacy during the cypress season as compared with the cedar season in the same year ($P < .001$; Fig 3, *C*).

Role of serum antigen–specific IgE levels in the efficacy of the cedar SLIT during the cypress season

In the present study, serum antigen–specific IgE levels were measured by the CAP, MAST, or View system. Among these, CAP is a quantitative method, whereas MAST and View are semiquantitative methods. Therefore, we analyzed the data using the CAP method.

We defined a positive result for specific allergens as a specific IgE level of 0.35 UA/mL or higher. Among the patients who had CAP IgE results for 5 allergens, the positive ratios for cedar, cypress, grass, birch, and dust mite were 100% (1460 of 1460 patients), 94% (1364 of 1451 patients), 51.7% (736 of 1424 patients), 48.6% (393 of 809 patients), and 68.4% (985 of 1441 patients), respectively.

Cedar- and cypress-specific IgE levels were significantly higher in the patients who had symptoms during the cypress season ($P = .010$ for both; Fig 4, *A* and *B*), whereas grass-, birch-, or dust mite–specific IgE levels did not exhibit any significant difference ($P = .153$, $P = .105$, and $P = .504$, respectively; Fig 4, *C-E*) as compared with those seen in patients who did not have any symptoms during the cypress season. In contrast, the IgE level for dust mite ($P = .028$) was significantly lower in patients reporting a lower efficacy (ineffective + relatively ineffective) for the cedar SLIT during the cypress season (Fig 5, *E*), whereas the

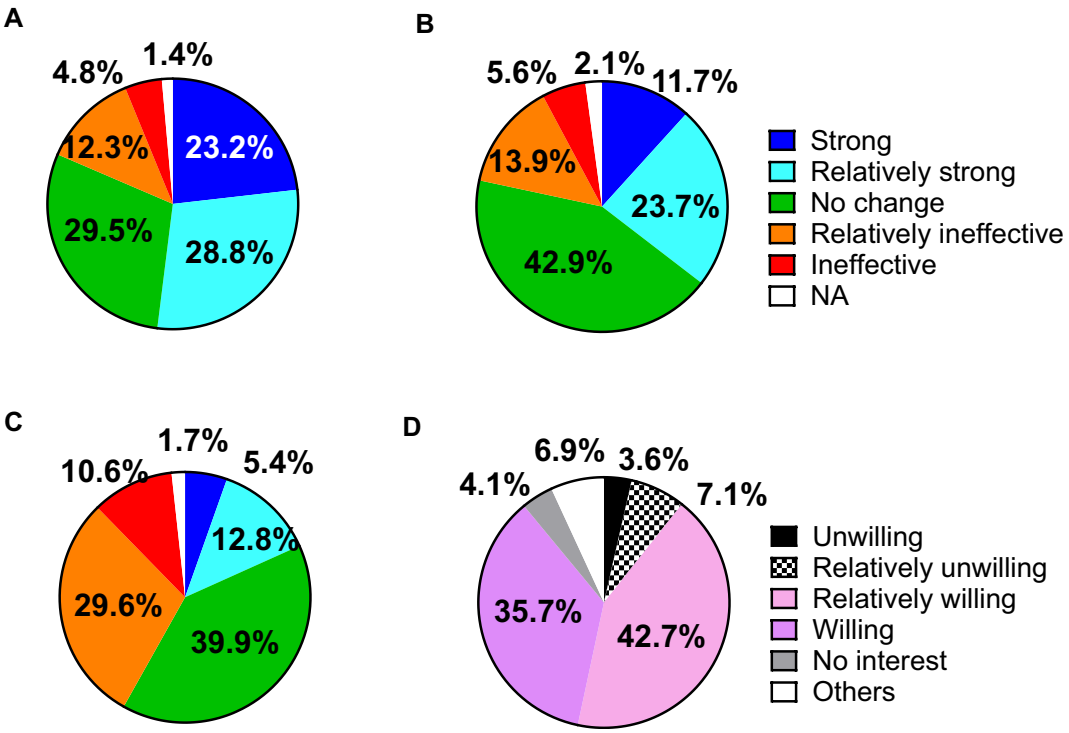

FIG 2. Summary of the answers to Q2 to Q5. **A** and **B,** The efficacy of cedar SLIT during the cedar (Fig 2, *A*) and cypress (Fig 2, *B*) seasons in 2023 as compared with that in 2022 (Q2 and Q3). **C,** The efficacy of cedar SLIT during the cypress season as compared with the cedar season in 2023 (Q4). **D,** Intention to receive cypress SLIT if it is developed (Q5). *NA,* Not applicable.

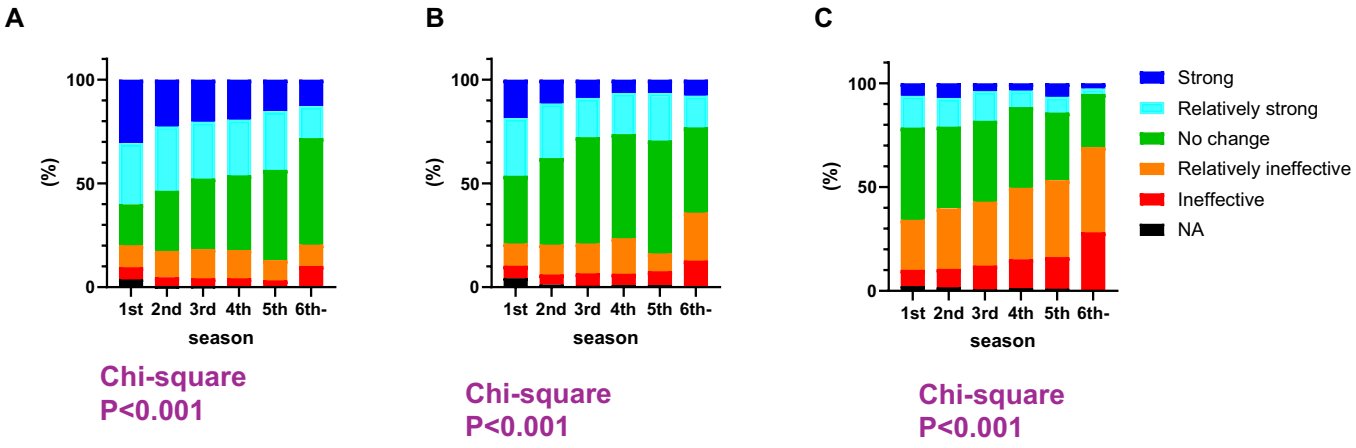

FIG 3. Yearly effectiveness of cedar SLIT. **A** and **B,** Yearly effectiveness of cedar SLIT during the cedar (Fig 3, *A*) and cypress (Fig 3, *B*) seasons. **C,** The efficacy of cedar SLIT during the cypress season as compared with the cedar season on the basis of the treatment period. The x-axis represents the season after the initiation of cedar SLIT. *NA,* Not applicable.

IgE levels for cedar (P = .907), cypress (P = .287), grass (P = .727), and birch (P = .318) were similar between the patients regardless of the efficacy for the cedar SLIT during the cypress season (Fig 5, *A-D*).

DISCUSSION

The results of this study demonstrated that among patients receiving cedar SLIT, 84.5% exhibited cypress pollinosis symptoms and 94% showed sensitization against cypress pollen. Priming or persistent mucosal inflammation due to cedar pollen exposure may affect rhinitis symptoms during the cypress season. However, the amount of cypress pollen dispersal varies and is usually lower than that of cedar pollen dispersal in eastern Japan. In fact, 15.5% of patients with cedar pollinosis did not experience rhinitis symptoms during the cypress season, suggesting that the effect of priming or persistent mucosal inflammation was negligible for them. One of the reasons why patients with cedar pollinosis tend to have comorbid cypress pollinosis is the high homologies found between the allergen components. The major

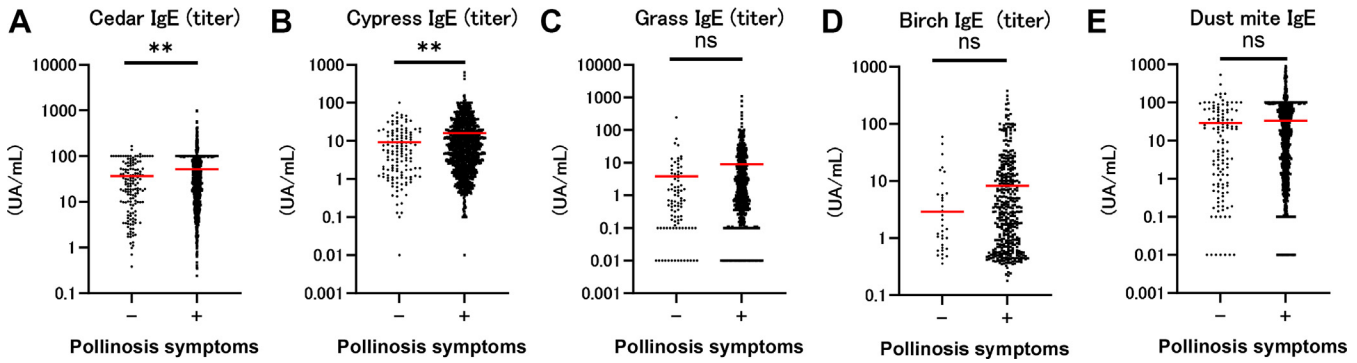

FIG 4. A-E, Comparison of serum CAP IgE for cedar (Fig 4, *A*), cypress (Fig 4, *B*), grass (Fig 4, *C*), birch (Fig 4, *D*), and dust mite (Fig 4, *E*) between the patients with and without pollinosis symptoms during the cypress season. The bar represents the mean. *NS,* Not significant. $^{**}P < .01$.

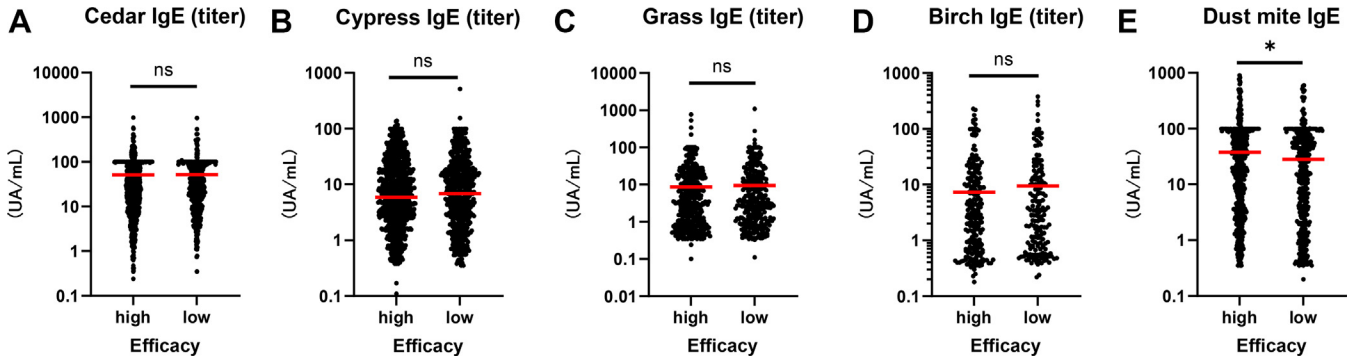

FIG 5. A-E, Comparison of serum CAP IgE for cedar (Fig 5, *A*), cypress (Fig 5, *B*), grass (Fig 5, *C*), birch (Fig 5, *D*), and dust mite (Fig 5, *E*) between the patients who reported high (more effective + relatively effective + similar) and low (ineffective + relatively ineffective) efficacy of the cedar SLIT during the cypress season. The bar represents the mean. $^{*}P < .05$.

allergen components of cedar pollen, Cry j 1, Cry j 2, and Cry j 4, are 80%, 74%, and 85% homologous to the major allergen components of the cypress pollen, Cha o 1, Cha o 2, and Cha o 3, respectively.[31-33] If the amino acid sequences of 2 allergens are more than 70% identical, these allergens are often cross-reactive.[34] This can also explain our results that showed that there was a strong positive correlation between the IgE levels for cedar and cypress ($r = 0.695$; $P < .001$; Fig E1, *B*). Previous studies have reported that the pollinosis ratios for cedar pollen in patients who also had symptoms and sensitization against cypress pollen were 70% and 86.7%, respectively, in Japan.[25,35] Another previous report[36] showed that the overlap of the sensitivities was 90.7% and is consistent between the present data (94%). Although the proportions in the present study were a little higher than those reported in the previous studies, it is possible that our results may have been affected by selection bias, because only those patients who had received the cedar SLIT were included in our study.

We reported in 2022 a multicenter clinical survey that examined the prevalence of Japanese cypress pollinosis and the efficacy of cedar SLIT during the cypress season.[20] The present study is a variant of this previous study and was conducted in 2023 to investigate the reproducibility and/or annual change. Our previous report showed that the ratios of patients with pollinosis symptoms caused by cedar pollen who also had symptoms and sensitization against cypress pollen were 83.4% and 94%, respectively. Our present results are consistent with this previous report and confirm the reproducibility during these 2 seasons.

The proportion of patients who felt there was a decreased efficacy of the cedar SLIT during the cypress season as compared with the cedar season in 2023 was 40.2% of those who had cypress pollinosis. Our present results are also consistent with our recent report in which we found that 37.4% of patients having cypress pollinosis experienced a lessened efficacy for the cedar SLIT during the cypress season.[20] One possible reason why the cedar SLIT does not induce a satisfactory effect on cypress pollinosis in a substantial number of patients may be the different amounts of allergen components that are present between the cedar and cypress pollen. Cha o 3 is the third major allergen component in Japanese cypress pollen, and this is the first allergen component that has a cellulase domain.[37] It is known that the amount of the component that is homologous to Cha o 3 in cedar pollen, Cry j 4, is low as compared with that for the Cha o 3 in cypress pollen.[33] These results suggest that the cedar SLIT may not induce an adequate immune tolerance to Cha o 3. In fact, Cha o 3–specific production of IL-10 by PBMCs and Cha o 3–specific IgG4 in serum were not increased in patients who had undergone cedar SLIT.[21] Another possibility regarding the ineffectiveness of the cedar SLIT for cypress pollinosis could be the high efficacy of the cedar SLIT for cedar pollinosis, because the causative and treatment pollen are identical.[38]

Subjects who were not receiving SLIT in 2022 showed much greater improvement in 2023 compared with those who were receiving treatment in 2022. Although the efficacy of the cedar SLIT during the cedar season was seen in 60% of patients during the first year, there was a decreased ratio of patients who felt there was a yearly improvement as compared with the previous season, with more than 70% of patients during the sixth year or more of treatment indicating that they did not feel there was a yearly improvement. This result agrees with other reports that have proposed that the optimal duration of SLIT ranges from 3 to 5 years.[3,39] In contrast, the longer the patients received cedar SLIT, proportionally the smaller the number reported year-to-year improvement in cypress season symptoms compared with the cedar season. This result also suggests the limitation of the cedar SLIT for cypress pollinosis. Thus, this may support the findings of our present study that found that 78.4% of patients would be open to undergoing a treatment with cypress SLIT if this were to become available, although standardized extract for cypress pollen is not commercially available so far in Japan.

About 50% to 80% of patients with allergy who receive treatments are polysensitized.[25-27] Even though we examined just 5 allergens, our present study also showed that three-quarters of the patients were sensitized to more than 3 allergens (Fig E1, *C*). Pollinosis symptoms during cypress season in Japan can be caused by various allergens including cypress, grass, birch, as well as house dust mite.[3] The IgE levels for cedar and cypress were significantly higher in patients with pollinosis symptoms during the cypress season as compared with those in patients without symptoms, whereas those for grass, birch, and dust mite did not differ between the groups. Minimal persistent inflammation caused by cedar pollen may be associated with the onset of cypress pollinosis.[40] These results suggest that the state of sensitization to grass, birch, and dust mite had a negligible effect on the symptoms during cypress season, and further suggest that the symptoms during cypress season are associated with allergic reactions to *Cupressaceae* pollen.

At the present time, it is debated as to whether SLIT is effective for polysensitized patients. Some studies have reported that SLIT monotherapy was effective in polysensitized patients.[41,42] A recent meta-analysis demonstrated that grass, ragweed, tree, and house dust mite SLIT-tablet treatment was effective in adults who were mono- or polysensitized.[43] Our present study demonstrated that the patients who experienced effectiveness of the cedar SLIT during the cypress season had significantly higher levels of IgE for dust mite. In addition, a significantly higher proportion of these patients who exhibited an efficacy of cedar SLIT received dust mite SLIT ($P < .001$; Fig E1, *D*), which suggests that use of a dual SLIT with dust mite and cedar extracts may have positive effects on cypress pollinosis because of the suppression of dust mite–induced nasal inflammation and subsequent hypersensitivity. However, sensitization against dust mite does not appear to have significant effects on the onset of pollinosis symptoms during the cypress season. Some reports have suggested that the ratio of the baseline allergen-specific IgE to total IgE could reflect the clinical efficacy of AIT.[44,45] Although we did not measure the serum total IgE, specific IgE levels for the 5 allergens that we examined were not elevated in patients who reported a lower efficacy of the cedar SLIT during the cypress season. Notably, dust mite–specific IgE was significantly lower in these patients. These results suggest that the decreased efficacy of cedar SLIT during the cypress season is not associated with the elevation of serum-specific IgE for inhaled allergens that exist during the cypress season, although dust mite SLIT may affect the efficacy of cedar SLIT.

There were some limitations to our present study. First, because IgE assays specific for components in cypress pollen such as Cha o 1, Cha o 2, and Cha o 3 and cross-reactive carbohydrate determinants are not commercially available in Japan, it was not possible to assess whether patients with symptoms during the cypress season actually responded to the cypress pollen components.[34] It should be noted that a cross-reactive carbohydrate determinant–related false-positive effect on the pollen-specific IgE has been noted in pollen screening.[46,47] Second, even though we recruited patients from eastern (n = 1611) and western (n = 986) Japan, the distribution of the collaboration facilities was still biased. The prevalence of cypress pollinosis and lessened efficacy of cedar SLIT on cypress pollinosis exhibit a regional difference in Japan,[20] which is compatible with the higher level of cypress pollen disperse in the western area compared with the eastern area of Japan.[29] Even though we recruited the subjects from eastern and western Japan, patients with severe and persistent symptoms, who may be targets for cypress immunotherapy, were likely to participate in this study. In addition, we did not include the number of patients who declined to be the subjects, although the number was small. Third, the questionnaire used in this study has not been validated, and further studies are needed to interpret the results with minimally important clinical differences. Fourth, recall bias may be present, because patients might perceive their pollinosis symptoms to be worse in 2023 compared with 2022, even though the severity of symptoms remains the same. Fifth, type 2 errors may be present because patients with severe symptoms might use any medication. Sixth, this study recruited only subjects receiving SLIT because the main purpose of this study was to determine the efficacy of cedar SLIT on cypress pollinosis. However, this patient selection may cause a bias in terms of the prevalence of cypress pollinosis and the role of serum-specific IgE levels in pollinosis. To exclude this bias, we are planning to collect Japan-wide data of cypress pollinosis including a non–SLIT-treated group in the next large study.

Most patients with cedar pollinosis have cypress pollinosis in which sensitization to grass, birch, and house dust mite exhibits negligible effects. About 40% of the patients in our present study felt there was a decreased efficacy of cedar SLIT during the cypress season as compared with the cedar season. In conjunction with the patients' expectations, development of an additional SLIT using standardized cypress crude antigen extract or Cha o 3 should be considered to potentially be able to attain substantial control of cypress pollinosis.

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Key messages

- **In a real-world setting, the proportion of cypress pollinosis in patients receiving cedar SLIT was 84.5%, and 40.2% of these patients felt a reduced efficacy of cedar SLIT on cypress pollinosis.**

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