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Original article

An analysis of factors related to the effect of sublingual immunotherapy on Japanese cedar pollen induced allergic rhinitis

Syuji Yonekura^a, Yoshitaka Okamoto^{a,*}, Daiju Sakurai^a, Kimihiro Okubo^b, Minoru Gotoh^c, Shinya Kaneko^d, Akiyoshi Konno^e^a Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan^b Department of Otolaryngology, Nippon Medical School, Tokyo, Japan^c Department of Otolaryngology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan^d Torii Pharmaceutical Co., Ltd., Tokyo, Japan^e Allergy and Head and Neck Tumor Center, Southern Tohoku General Hospital, Fukushima, Japan

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Abbreviations:

AIT, allergen-specific immunotherapy;

AR, allergic rhinitis; BMI, body mass index;

HDM, house dust mite; JC, Japanese cedar;

slgE/tIgE, specific IgE/total IgE;

SLIT, sublingual immunotherapy;

SCIT, subcutaneous immunotherapy;

TNSMS, total nasal symptom medication score

ABSTRACT

Background: Sublingual immunotherapy (SLIT) can improve the symptoms of allergic rhinitis and modify its natural history; however, its efficacy varies among patients. This study aimed to determine which factors modify the effect of SLIT through post hoc analysis of a previous phase 3 trial of standardized Japanese cedar (JC) pollen extract (CEDARTOLEN®).

Methods: The study included 482 patients who had previously completed a phase 3 trial during two seasons. The SLIT and placebo groups each contained 241 subjects. Because pollen dispersal differed in the two seasons, we identified good and poor responders from the SLIT group in the 2nd season. We compared patient baseline characteristics, changes in serum immunoglobulin, and severity of symptoms in the 1st season between good and poor responders, as well as between SLIT and placebo groups.

Results: When we compared the baseline characteristics of good and poor responders, a significant difference was observed in body mass index (BMI) such that the patients with BMI ≥ 25 presented with lower treatment efficacy. No significant difference was observed in correlation with any other factors or treatment-induced alterations of serum immunoglobulin levels. We found that 75.3% of the patients with moderate symptoms and 50.9% of the patients with severe or very severe symptoms in the 1st season met our criteria for good responders in the 2nd season.

Conclusions: BMI might modify the effect of SLIT; however, other factors were not related clearly. The severity of symptoms in the 1st season of treatment does not predict that in the 2nd season.

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Introduction

Allergen-specific Immunotherapy (AIT) can modify the natural history of allergic rhinitis (AR) and has become an indispensable therapy for this disease.^{1–3} Relative to subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT) reduces the burden to patients, because it eliminates the need for frequent

injections and hence the associated pain and inconvenience and because it decreases severe side effects.

In Japan, Japanese cedar (JC) pollen is the pollen allergen that most commonly induces widespread AR.^{4–7} Clinical studies of SLIT for JC pollen induced AR have been conducted in small populations of patients, and efficacy and safety of the therapy have been confirmed.^{8–10} In addition, a large, randomized phase 3 trial of a standardized JC pollen extract administered as an oral formulation (CEDARTOLEN®) was conducted from 2010 to 2012 during two consecutive pollination seasons.¹¹ In this study, the total nasal symptom medication score (TNSMS) of the SLIT group in the 2nd season, the primary endpoint, was approximately 30% lower than in the placebo group.

* Corresponding author. Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan.

E-mail address: yokamoto@faculty.chiba-u.jp (Y. Okamoto).

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Although SLIT is an effective treatment for AR, its efficacy varies across patients. It is known to be ineffective in a certain proportion of patients. Although SLIT places relatively lesser burden on patients compared with SCIT, the duration of treatment remains lengthy. Thus, identifying any factor that affects the efficacy of SLIT, either among baseline characteristics or among those determined through easy screening, is important for predicting individual efficacy.

A high rate of placebo effects was observed in previous SLIT studies.¹² In the previous phase 3 trial, 39.4% of patients in the placebo group had mild symptoms during the peak pollen dispersal in the 2nd season compared with 61.0% of patients in the SLIT group.¹¹ Thus, the placebo effect should have significantly influenced the SLIT group, and the distinction between actual responder and non-responder was difficult. However, because this trial was conducted for two consecutive pollination seasons with appreciably different amounts of pollen dispersal, we were able to perform a secondary data analysis by identifying good and poor responders to SLIT and evaluate the factors associated with a good response.

The aim of this study is to retrospectively examine the factors that could affect the efficacy of SLIT. Therefore, we performed a secondary analysis of these factors: baseline characteristics, changes of serum immunoglobulin, and severity of the 1st season AR symptoms for the patients who completed the treatment in the previous phase 3 trial. Specifically, this study examined differences between good and poor responder groups from within the active SLIT groups, as well as between SLIT and placebo groups.

Methods

The previous phase 3 trial

The study design was a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study, as reported previously.¹¹ Briefly, patients with JC pollen induced AR, aged from 12 to 64 years old, were enrolled; those who had other types of rhinitis or needed to receive treatments were excluded.

A maintenance dose of 1 ml of 2000 JAU/ml was administered to the subjects every day in the SLIT group for 18 months from October 2010 to April 2012 during two consecutive pollination seasons. JC pollen dispersal typically starts in early February and lasts for 10 weeks in Tokyo. The JC pollen count was measured with the Durham method at the Chiyoda ward in Tokyo. In 2011, during the season from February 17 to May 16 (89 days), the JC pollen count was 6537/cm² with the highest reported spread being 588/cm² on March 16. In 2012, during the season from March 3 to April 27 (56 days), the JC pollen count was 1256/cm², which was much lower than the previous season. The highest pollen spread recorded in this season was 159/cm² on March 7.

The 531 patients with JC pollen induced AR were randomized into the SLIT (n = 266) and placebo (n = 265) groups. The same number of subjects in each group (n = 241) completed the study in 2012. Scores were obtained for three types of nasal symptoms: sneeze, rhinorrhea, and nasal congestion using a 5-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe) based on the Japanese guidelines for AR.¹³ The total nasal symptom score was calculated as the sum of the three symptom scores (range: 0–12). The use of rescue drugs (fexofenadine hydrochloride or tramazoline hydrochloride) was scored as 0 (not used) or 3 (used), and a total nasal medication score, sum for both drugs, was calculated (range: 0–6). The primary endpoint was the total nasal symptom plus the medication score (TNSMS; range: 0–18) during the peak symptom period in the 2nd season.

Serum IgE, JC pollen-specific IgE and IgG4 were measured at 7 time points: before the initiation of dosing, and before, in the middle, and at the end of the JC pollination seasons in 2011 and 2012. In the 1st season, the time point chosen to represent before the pre-season was 2 months after the initiation of immunotherapy. More precisely, the 7 time points were from September to December, 2010 (before the initiation of dosing), December, 2010 (before the 1st season), the first half of March, 2011 (middle of the 1st season), May, 2011 (at the end of the 1st season), December, 2011 (before the 2nd season), the first half of March, 2012 (middle of the 2nd season) and May, and 2012 (at the end of the 2nd season). Assays were conducted at Mitsubishi Chemical Medience (Tokyo, Japan).

Subjects of the secondary, post hoc analysis

The subjects of the current analysis were 482 patients who completed the previous phase 3 trial during two consecutive pollination seasons. Each group included the same number of subjects (n = 241).

Comparison of TNSMSs between treatment and placebo groups for baseline demographic, clinical and laboratory characteristics

The following baseline characteristics were assessed: gender, age, height, weight, body mass index (BMI), duration of JC pollen induced AR, family history of JC pollen induced AR and other allergic diseases, total IgE level, JC pollen-specific IgE level, house dust mite (HDM)-specific IgE level, and sensitization to other allergens besides JC pollen. TNSMSs were compared between SLIT and placebo groups for each baseline characteristic.

Comparison of TNSMS and the baseline characteristics between good and poor responders identified within the SLIT group

The severity of each patient for the two pollination seasons was determined. The severity category was based on the TNSMS in the peak symptom period and defined as: mild, TNSMS ≤ 4; moderate, 4 < TNSMS ≤ 7; severe, 7 < TNSMS ≤ 10; and very severe, TNSMS > 10. The good responder group included patients whose severity was moderate, severe, or very severe in the 1st season and improved to mild in the 2nd season, and patients whose severity level was very severe in the 1st season and improved to moderate in the 2nd season. The poor responder group included patients

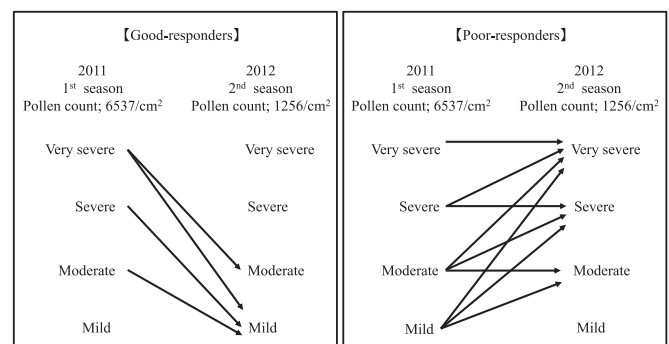


Fig. 1. Definitions of good and poor responder groups. The severity category was based on the TNSMS in the peak symptom period and defined as: mild, TNSMS ≤ 4; moderate, 4 < TNSMS ≤ 7; severe, 7 < TNSMS ≤ 10; and very severe, TNSMS > 10. The good responder group included patients whose severity was moderate, severe, or very severe in the 1st season and improved to mild in the 2nd season and patients whose severity level was very severe in the 1st season and improved to moderate in the 2nd season. The poor responder group included patients whose severity remained the same or worsened from the 1st season to the 2nd season.

whose severity remained the same or worsened from the 1st season to the 2nd season (Fig. 1).

Considering smaller pollen level of 2nd season than 1st season, we classified the patient whose severity was greatly improved in 2nd season into good responder group. In regard to the patients whose severity was mild in the both 1st and 2nd seasons, there was possibility that their severity had already been improved in 1st season or had been mild even before the treatment. To remove cases like the latter, we did not classify them into good responder group.

TNSMSs, baseline characteristics, and changes of serum JC pollen-specific IgE and IgG4 were compared between good and poor responders selected from the SLIT group. For comparison of the baseline characteristics, JC pollen-specific IgE/total IgE (sIgE/tIgE) ratio was added to the former characteristics.

Statistical analysis

The student t-test and the chi-square test were used for comparison of baseline characteristics and TNSMSs between the SLIT and placebo groups. The change of TNSMSs of good and poor responders was analyzed using a paired Student t-test. The chi-square test was also used to compare baseline characteristics between the good and poor responder groups. For serum immunoglobulin, changes of titers within good and poor responder groups and the comparison of titers between the two groups were analyzed by a paired and non-paired student t-test, respectively. Data analysis was performed with each statistical method at a 5% significant level using SPSS statistics base 23[®].

Results

Baseline characteristics of 482 subjects who completed the previous phase 3 trial

Baseline characteristics of the subjects in each group are shown in Table 1. There were no significant differences between the two groups in the baseline characteristics except that the proportion of patients who were sensitized to allergens other than the JC pollen was significantly higher in the placebo group than in the SLIT group ($p < 0.05$).

Table 1

Baseline characteristics of 482 subjects who completed the previous phase 3 trial.

Backgrounds		Active SLIT group (n = 241)	Placebo SLIT group (n = 241)	P-value
Gender	Female (n, %)	147 (61.0)	152 (63.1)	.64
	Male (n, %)	94 (39.0)	89 (36.9)	
Age, years	Mean (SD)	40.8 (11.3)	40.2 (10.1)	.58
Height, cm	Mean (SD)	162.6 (8.7)	162.9 (8.4)	.62
Weight, kg	Mean (SD)	58.9 (11.8)	58.5 (11.2)	.70
BMI	Mean (SD)	22.2 (3.3)	22.0 (3.6)	.53
Disease duration of JC pollen induced AR, years	Mean (SD)	16.0 (9.1)	16.7 (8.4)	.37
Family history of JC pollen induced AR	Yes, n (%)	146 (60.6)	151 (62.7)	.64
	No, n (%)	95 (39.4)	90 (37.3)	
Family history of other allergic diseases [†]	Yes, n (%)	100 (41.5)	98 (40.7)	.85
	No, n (%)	141 (58.5)	143 (59.3)	
Total IgE, IU/ml	Mean (SD)	229.8 (444.6)	232.3 (361.8)	.95
JC pollen-specific IgE, UA/ml	Mean (SD)	24.4 (24.3)	25.6 (26.0)	.61
JC pollen-specific IgE level	Class 3, n (%)	140 (58.1)	126 (52.3)	.42
	Class 4, n (%)	70 (29.0)	82 (34.0)	
	Class 5, 6, n (%)	31 (12.9)	33 (13.7)	
	Class 0, 1, n (%)	159 (66.0)	156 (64.7)	
HDM-specific IgE level	Class 2≤, n (%)	82 (34.0)	85 (35.3)	.77
	Class 0, 1, n (%)	159 (66.0)	156 (64.7)	
Sensitization of other allergen [‡]	Yes, n (%)	172 (71.4)	192 (79.7)	<.05
	No, n (%)	69 (28.6)	49 (20.3)	

[†] Perennial allergic rhinitis, bronchial asthma, atopic dermatitis.

[‡] HDM, cypress, alder, birch, orchard grass, ragweed, mugwort, alternaria, candida, aspergillus.

Comparison of TNSMSs of each baseline characteristic between the SLIT and placebo groups

Table 2 shows the comparison of TNSMSs across each baseline characteristic. For most of baseline subgroups, TNSMS means of the SLIT group were significantly lower than the means of the placebo group. However, no significant difference was found in TNSMSs between the SLIT and placebo groups for three subgroups: height ≥ 170 , weight ≥ 70 kg, and BMI ≥ 25 ($p = 0.12$, $p = 0.79$, and $p = 0.73$, respectively). Although mean TNSMS was lower in the SLIT group than in the placebo group, in the subgroup for whose total IgE levels were high, >173 IU/ml, in this subgroup there was no significant difference in TNSMS between the SLIT and placebo groups ($p = 0.052$).

TNSMS in good and poor responders identified within the SLIT group

The numbers of subjects who were identified as good and poor responder groups were 118 and 42, respectively. Changes of TNSMSs of the good and poor responder groups are shown in Table 3. The mean TNSMS of the good responder group in the 2nd season, 2.79, was significantly lower than the mean TNSMS, 7.69, in the 1st season ($p < 0.0001$). The TNSMS means of the poor responder group in the 1st and 2nd seasons were 7.94 and 7.86, respectively. As expected from the definition of the poor responder group, significant improvement was not shown in the poor responder group in the 2nd season compared with the 1st season. Across all baseline characteristics, significant improvement was shown in the good responder group in the 2nd season compared with the 1st season but not in the poor responder group.

Comparison of baseline characteristics between good and poor responders identified within the SLIT group

Table 4 shows the comparison of baseline characteristics. No significant difference was found between the good and poor responder groups across all baseline characteristics except BMI. The proportion of good responders in the BMI group of ≥ 25 was lower than the group of <25 and a significant difference was observed between good and poor responders ($p < 0.001$). The proportion of good responders in the height group of ≥ 170 cm and weight group

Table 2

Comparison of TNSMSs of each baseline characteristic in the 2nd season between the SLIT and placebo groups.

Backgrounds		Total number	SLIT group n = 241		Placebo group n = 241		Difference [†] (95% CI)	P-value
			n (%)	Mean TNSMS	n (%)	Mean TNSMS		
Gender	Female	299	147 (49.2)	3.81	152 (50.8)	5.94	−2.13 (−2.89 to −1.37)	<.0001
	Male	183	94 (51.4)	4.29	89 (48.6)	5.32	−1.02 (−2.02 to −0.03)	<.05
Age, years	<40	209	100 (47.8)	4.02	109 (52.2)	5.97	−1.95 (−2.91 to −0.99)	<.0001
	40≤	273	141 (51.6)	3.98	132 (48.4)	5.49	−1.51 (−2.29 to −0.73)	<.001
Height, cm	<160	191	100 (52.4)	3.85	91 (47.6)	5.70	−1.85 (−2.76 to −0.93)	<.0001
	<170	184	89 (48.4)	3.83	95 (51.6)	5.74	−1.91 (−2.89 to −0.92)	<.001
Weight, kg	170≤	107	52 (48.6)	4.56	55 (51.4)	5.67	−1.11 (−2.51 to 0.29)	.12
	<50	113	60 (53.1)	3.42	53 (46.9)	5.79	−2.38 (−3.58 to −1.17)	<.001
	<60	175	81 (46.3)	3.91	94 (53.7)	6.20	−2.30 (−3.33 to −1.26)	<.0001
	<70	122	65 (53.3)	4.09	57 (46.7)	5.40	−1.31 (−2.43 to −0.20)	<.05
BMI	70≤	72	35 (48.6)	5.03	37 (51.4)	4.80	0.23 (−1.49 to 1.95)	.79
	<20	137	62 (45.3)	3.75	75 (54.7)	6.04	−2.29 (−3.54 to −1.03)	<.001
	<25	263	135 (51.3)	3.87	128 (48.7)	5.72	−1.85 (−2.58 to −1.11)	<.0001
	25≤	82	44 (53.7)	4.72	38 (46.3)	5.01	−0.29 (−1.95 to 1.37)	.73
Disease duration of JC pollen induced AR, years	<10	114	65 (57.0)	3.66	49 (43.0)	5.52	−1.87 (−3.01 to −0.73)	<.01
	<20	198	99 (50.0)	4.07	99 (50.0)	6.16	−2.09 (−3.06 to −1.13)	<.0001
Family history of JC pollen induced AR	20≤	170	77 (45.3)	4.20	93 (54.7)	5.32	−1.13 (−2.18 to −0.07)	<.05
	Yes	297	146 (49.2)	4.08	151 (50.8)	5.77	−1.69 (−2.48 to −0.90)	<.0001
Family history of other allergic disease [‡]	No	185	95 (51.4)	3.87	90 (48.6)	5.60	−1.73 (−2.66 to −0.80)	<.001
	Yes	198	100 (50.5)	3.86	98 (49.5)	5.86	−2.00 (−2.89 to −1.12)	<.0001
Total IgE, IU/ml [‡]	No	284	141 (49.6)	4.10	143 (50.4)	5.60	−1.51 (−2.33 to −0.68)	<.001
	≤173	323	167 (51.7)	4.04	156 (48.3)	6.22	−2.18 (−2.96 to −1.40)	<.0001
JC pollen-specific IgE level	173<	159	74 (46.5)	3.89	85 (53.5)	4.76	−0.88 (−1.76 to 0.01)	.052
	Class 3	266	140 (52.6)	3.85	126 (47.4)	5.90	−2.04 (−2.89 to −1.20)	<.0001
HDM-specific IgE level	Class 4	152	70 (46.1)	4.37	82 (53.9)	5.55	−1.18 (−2.25 to −0.10)	<.05
	Class 5, 6	64	31 (48.4)	3.80	33 (51.6)	5.38	−1.58 (−3.02 to −0.15)	<.05
Sensitization of other allergen [§]	Class 0, 1	315	159 (50.5)	4.23	156 (49.5)	6.13	−1.91 (−2.69 to −1.12)	<.0001
	Class 2≤	167	82 (49.1)	3.55	85 (50.9)	4.92	−1.37 (−2.27 to −0.48)	<.01
	Yes	364	172 (47.3)	3.90	192 (52.7)	5.76	−1.86 (−2.57 to −1.15)	<.0001
	No	118	69 (58.5)	4.24	49 (41.5)	5.49	−1.25 (−2.42 to −0.08)	<.05

[†] Perennial allergic rhinitis, bronchial asthma, atopic dermatitis.[‡] Reference value of total IgE is ≤173 IU/ml.[§] HDM, cypress, alder, birch, orchard grass, ragweed, mugwort, alternaria, candida, aspergillus.[¶] (TNSMS in the SLIT group) − (TNSMS in the placebo group).

of ≥70 kg tended to be lower; however, no significant difference was shown for either of these physical characteristics.

Comparison of changes in serum immunoglobulins between good and poor responders identified within the SLIT group

The changes in serum levels of JC pollen-specific IgE and IgG4 are shown in Figure 2. The JC pollen-specific IgE level increased significantly two months after the start of treatment. The level of JC-specific IgE remained elevated until the end of the 1st season. In the 2nd season, this level did not increase at the end of the season compared with levels that preceded the start of the season. Similarly, the level of JC pollen-specific IgG4 increased significantly two months after the start of treatment and increased after the 1st season. This level gradually decreased until the end of the 2nd season but still remained higher than the baseline level measured before the start of the 1st season. The changes of these JC pollen-specific antibodies did not differ significantly between the two groups at any time point assessed.

Comparison of disease severity between the 1st and 2nd seasons

In the SLIT group, the good responder group included 28, 26, and 64 cases with severities of very severe, severe, and moderate in the 1st season, respectively (Table 5). Conversely, the poor responder group included 8, 9, 21, and 4 cases with severities of very severe, severe, moderate, and mild in the 1st season, respectively. The percentage of good responders was 75.3% (64/85) among cases with moderate severity in the 1st season and was 50.9% (54/106)

among cases that showed very severe or severe symptoms in the 1st season.

In the placebo group, the numbers of subjects who were identified as good and poor responder groups were 102 and 67, respectively. The percentage of good responders was 64.9% (37/57) among cases with moderate severity in the 1st season and was 42.2% (65/154) among cases that showed very severe or severe symptoms in the 1st season.

Discussion

In the current study, we performed a post hoc analysis of the baseline characteristics of 482 patients who completed treatment in the previous phase 3 trial and retrospectively examined whether the baseline characteristics affected the efficacy of SLIT. TNSMSs of the SLIT group were significantly lower than those for the placebo for most of examined subgroups defined by baseline characteristics. These results suggest that JC pollen extract used in the previous phase 3 trial was effective in most patients, regardless of their baseline characteristics.

A unique feature of the study was our analysis of differences between good and poor responder groups identified among the SLIT group. It is difficult to accurately evaluate the efficacy of SLIT for pollen induced AR. The primary source of this difficulty is the annual variability of the airborne pollen counts. In this trial, JC pollen counts were 6537/cm² and 1256/cm² in the 1st and 2nd seasons, respectively, while the mean pollen count in Tokyo in the last 10 years is 3200/cm². Another source of difficulty when determining the efficacy of AR treatment is the large placebo effect.

Table 3

TNSMS in good and poor responders identified within the SLIT group.

Backgrounds		Good-responders n = 118					Poor-responders n = 42				
		Mean TNSMS					Mean TNSMS				
		n	2011	2012	Difference (95% CI)	P-value	n	2011	2012	Difference (95% CI)	P-value
Total		118	7.69	2.79	-4.89 (-5.41 to -4.38)	<.0001	42	7.94	7.86	-.08 (-0.60 to 0.43)	.75
Gender	Female	77	7.85	2.75	-5.10 (-5.77 to -4.44)	<.0001	25	7.74	7.42	-.32 (-1.00 to 0.36)	.34
	Male	41	7.38	2.88	-4.50 (5.33 to -3.67)	<.0001	17	8.23	8.50	0.27 (-0.58 to 1.11)	.51
Age, years	<40	48	7.68	2.69	-4.99 (-5.75 to -4.24)	<.0001	16	8.18	8.54	0.36 (-0.48 to 1.20)	.37
	40≤	70	7.69	2.87	-4.82 (-5.54 to -4.11)	<.0001	26	7.79	7.44	-.36 (-1.03 to 0.32)	.29
Height, cm	<160	50	8.04	2.89	-5.16 (-6.04 to -4.27)	<.0001	19	7.11	7.21	0.11 (-0.58 to 0.79)	.75
	<170	47	7.23	2.62	-4.61 (-5.38 to -3.84)	<.0001	13	9.15	8.29	-.87 (-1.85 to 0.12)	.080
	170≤	21	7.86	2.96	-4.89 (-6.08 to -3.71)	<.0001	10	7.94	8.52	0.58 (-0.73 to 1.89)	.34
Weight, kg	<50	38	7.45	2.68	-4.77 (-5.69 to -3.85)	<.0001	7	7.82	7.46	-.36 (-1.69 to 0.97)	.53
	<60	34	8.55	2.84	-5.71 (-6.87 to -4.55)	<.0001	14	7.32	7.24	-.08 (-0.99 to 0.83)	.85
	<70	35	7.06	2.72	-4.34 (-5.08 to -3.60)	<.0001	14	7.40	7.71	0.31 (-0.77 to 1.39)	.54
	70≤	11	7.84	3.29	-4.55 (-6.57 to -2.54)	<.001	7	10.39	9.79	-.60 (-2.14 to 0.95)	.38
BMI	<20	33	7.52	2.64	-4.88 (-5.97 to -3.80)	<.0001	11	8.59	8.27	-.32 (-1.33 to 0.70)	.51
	<25	70	7.64	2.85	-4.79 (-5.42 to -4.16)	<.0001	17	6.74	7.02	0.28 (-0.54 to 1.10)	.48
	25≤	15	8.26	2.88	-5.39 (-7.19 to -3.58)	<.0001	14	8.88	8.55	-.34 (-1.40 to 0.73)	.51
Disease duration of JC pollen induced AR, years	<10	30	7.32	2.63	-4.70 (-5.85 to -3.54)	<.0001	9	6.58	6.56	-.02 (-1.39 to 1.34)	.97
	<20	55	7.80	2.98	-4.82 (-5.54 to -4.10)	<.0001	17	8.20	8.28	0.07 (-0.77 to 0.91)	.86
	20≤	33	7.83	2.64	-5.19 (-6.22 to -4.16)	<.0001	16	8.42	8.14	-.28 (-1.17 to 0.61)	.51
Family history of JC pollen induced AR	Yes	74	7.55	2.63	-4.92 (-5.55 to -4.29)	<.0001	24	8.88	8.72	-.16 (-0.88 to 0.56)	.66
	No	44	7.92	3.08	-4.85 (-5.77 to -3.92)	<.0001	18	6.69	6.71	0.02 (-0.79 to 0.82)	.97
Family history of other allergic disease [†]	Yes	52	8.17	2.94	-5.23 (-6.06 to -4.39)	<.0001	13	8.15	7.63	-.52 (-1.59 to 0.56)	.31
	No	66	7.31	2.68	-4.63 (-5.29 to -3.97)	<.0001	29	7.85	7.96	0.11 (-0.49 to 0.71)	.70
Total IgE, IU/ml [‡]	≤173	83	7.80	2.80	-5.01 (-5.63 to -4.38)	<.0001	29	8.38	8.08	-.30 (-0.92 to 0.32)	.33
	173<	35	7.42	2.79	-4.62 (-5.58 to -3.67)	<.0001	13	6.95	7.36	0.40 (-0.59 to 1.40)	.40
JC pollen-specific IgE level	Class 3	71	7.90	2.86	-5.04 (-5.72 to -4.36)	<.0001	23	8.30	7.97	-.32 (-1.09 to 0.44)	.39
	Class 4	29	7.30	2.78	-4.52 (-5.55 to -3.49)	<.0001	15	7.27	7.62	0.34 (-0.45 to 1.14)	.37
	Class 5, 6	18	7.48	2.57	-4.91 (-6.40 to -3.42)	<.0001	4	8.39	8.10	-.30 (-3.13 to 2.54)	.76
JC pollen-specific IgE/Total IgE ratio [§]	<0.19	69	7.21	2.64	-4.57 (-5.19 to -3.94)	<.0001	24	7.14	7.48	0.34 (-0.35 to 1.03)	.32
	0.19≤	49	8.36	3.01	-5.35 (-6.24 to -4.46)	<.0001	18	9.00	8.36	-.65 (-1.41 to 0.11)	.091
HDM-specific IgE level	Class 0, 1	80	7.89	2.89	-5.00 (-5.63 to -4.38)	<.0001	29	8.54	8.35	-.20 (-0.85 to 0.45)	.54
	Class 2≤	38	7.26	2.60	-4.66 (-5.61 to -3.71)	<.0001	13	6.60	6.77	0.17 (-0.75 to 1.10)	.69
Sensitization of other allergen [¶]	Yes	79	7.17	2.64	-4.53 (-5.11 to -3.94)	<.0001	30	7.44	7.62	0.18 (-0.44 to 0.80)	.55
	No	39	8.74	3.10	-5.63 (-6.65 to -4.62)	<.0001	12	9.19	8.44	-.75 (-1.69 to 0.20)	.11

[†] Perennial allergic rhinitis, bronchial asthma, atopic dermatitis.[‡] Reference value of total IgE is ≤173 IU/ml.[§] Mean value of JCP IgE/total IgE ratio was 0.19.[¶] HDM, cypress, alder, birch, orchard grass, ragweed, mugwort, alternaria, candida, aspergillus.^{||} (TNSMS in 2012) - (TNSMS in 2011).

The placebo effect would significantly influence even the SLIT group, making the distinction between actual responder and non-responder difficult. However, the placebo effect is not associated with the effects of SLIT and should contribute to the early recurrence of symptoms.

Although it was ideal to examine the severity of patients precisely before the trial and judge the treatment effect, we were not able to know their accurate severity beforehand. In this analysis, considering the different amount of pollen dispersal, we selected good responders as the patients whose severity decreased by two or three severity categories or decreased to mild in the 2nd season compared with the 1st season. The patients whose severity slightly decreased were not selected because we attributed this small change to the influence of the relatively small pollen level in the 2nd season. Conversely, identification of patients for whom SLIT was ineffective was simple; those whose severity did not improve in the 2nd season were defined as poor responders. Although SLIT may be very effective in the patients whose severity was mild in the both 1st and 2nd seasons, we did not define them as good responders because their severity may have been mild even before the treatment.

When we compared the baseline characteristics between the good and poor responders in the SLIT group, it was evident that the treatment was significantly less effective in patients with BMI ≥25 as compared to those with BMI <25. It is generally known that

obesity is associated with aggravation or poor control of asthma.^{14,15} however, the exact influence of obesity in AR has not been reported. Interestingly, a nationwide study in United States reported that obesity was not associated with increased odds of AR.¹⁶ The International Study of Asthma and Allergies in Childhood phase two study confirmed that BMI was associated with an objective marker of airways obstruction; however, no such markers for respiratory and allergic disorders including rhinitis are available.¹⁷ Although the association between BMI and efficacy of SLIT has not been reported so far, the results of this study may reflect the insufficient doses of the cedar allergens. In the development of CEDARTOLEN[®] for SLIT, the dose-escalation study has not been done. Recent study with house dust mite tablets in an environmental exposure chamber showed a dose-dependent improvement of SLIT.¹⁸ The maintenance dose used in the current 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. The maintenance dose was less than the dose of 600 µg/month used in a large clinical study of sublingual glass pollen tablets.¹⁹ Further studies using higher doses of cedar allergen might be necessary to improve the efficacy.

It is important to decide whether SLIT should be continued in patients without clear benefit from SLIT in the 1st season. We found that 75.3% of the patients with moderate symptoms and 50.9% of the patients with severe or very severe symptoms in the 1st season

Table 4
Comparison of baseline characteristics between good and poor responders identified within the SLIT group.

Backgrounds		Total number	Good-responders, n = 118 n (%)	Poor-responders, n = 42 n (%)	P-value
Gender	Female	102	77 (75.5)	25 (24.5)	.51
	Male	58	41 (70.7)	17 (29.3)	
Age, years	<40	64	48 (75.0)	16 (25.0)	.77
	40≤	96	70 (72.9)	26 (27.1)	
Height, cm	<160	69	50 (72.5)	19 (27.5)	.53
	<170	60	47 (78.3)	13 (21.7)	
	170≤	31	21 (67.7)	10 (32.3)	
Weight, kg	<50	45	38 (84.4)	7 (15.6)	.21
	<60	48	34 (70.8)	14 (29.2)	
	<70	49	35 (71.4)	14 (28.6)	
	70≤	18	11 (61.1)	7 (38.9)	
BMI	<20	44	33 (75.0)	11 (25.0)	<.001
	<25	87	70 (80.5)	17 (19.5)	
	25≤	29	15 (51.7)	14 (48.3)	
	<10	39	30 (76.9)	9 (23.1)	
Disease duration of JC pollen induced AR, years	<20	72	55 (76.4)	17 (23.6)	.47
	20≤	49	33 (67.3)	16 (32.7)	
	Yes	98	74 (75.5)	24 (24.5)	.52
Family history of JC pollen induced AR	No	62	44 (71.0)	18 (29.0)	
Family history of other allergic disease [†]	Yes	65	52 (80.0)	13 (20.0)	.14
	No	95	66 (69.5)	29 (30.5)	
Total IgE, IU/ml [‡]	≤173	112	83 (74.1)	29 (25.9)	.88
	173<	48	35 (72.9)	13 (27.1)	
JC pollen-specific IgE score	Class 3	94	71 (75.5)	23 (24.5)	.32
	Class 4	44	29 (65.9)	15 (34.1)	
	Class 5, 6	22	18 (81.8)	4 (18.2)	
JC pollen-specific IgE/total IgE ratio [§]	<0.19	93	69 (74.2)	24 (25.8)	.88
	0.19≤	67	49 (73.1)	18 (26.9)	
HDM-specific IgE score	Class 0, 1	109	80 (73.4)	29 (26.6)	.88
	Class 2<	51	38 (74.5)	13 (25.5)	
Sensitization of other allergen [¶]	Yes	109	79 (72.5)	30 (27.5)	.59
	No	51	39 (76.5)	12 (23.5)	

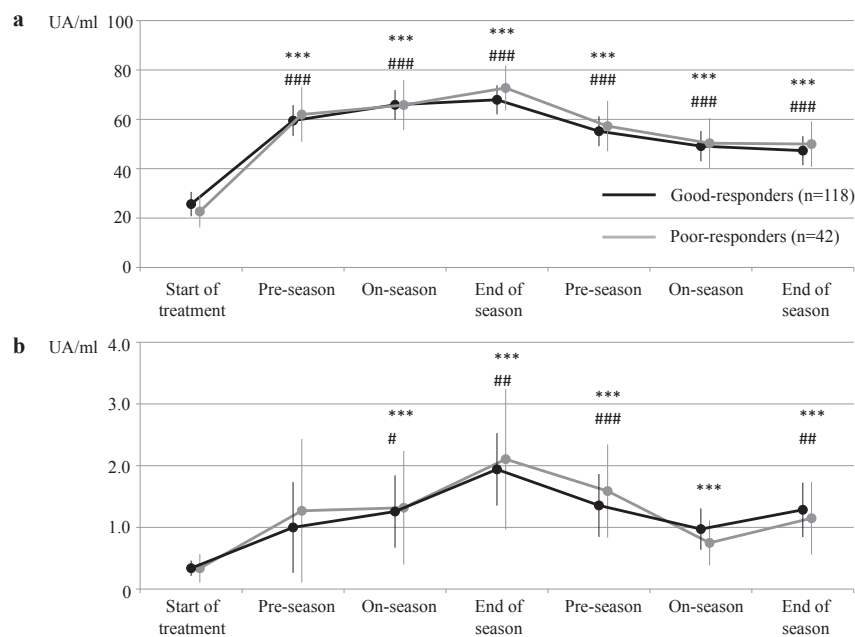
[†] Perennial allergic rhinitis, bronchial asthma, atopic dermatitis.[‡] Reference value of total IgE is ≤173 IU/ml.[§] Mean value of JCP IgE/total IgE ratio was 0.19.[¶] HDM, cypress, alder, birch, orchard grass, ragweed, mugwort, alternaria, candida, aspergillus.**Fig. 2.** Changes in serum levels of JC-specific IgE (a) and IgG4 (b). The changes of JC pollen-specific antibodies were similar between the good and poor responder groups, and the levels did not differ significantly between the groups at any time point assessed. In both good and poor responders, after starting SLIT their JC pollen-specific antibody levels increased significantly relative to baseline levels. The marker and error bar shows mean value and 95% CI, respectively. Good responders, ****p* < 0.001. Poor responders, #*p* < 0.05; ##*p* < 0.01; ###*p* < 0.001.

Table 5

Comparison of disease severity between the 1st and 2nd seasons.

	Severity in the 1st season Pollen count: 6537/cm ²	Severity in the 2nd season Pollen count: 1256/cm ²	SLIT group n = 241	Placebo group n = 241
Good-responder	Very severe	Moderate/mild	28	46
	Severe	Mild	26	19
	Moderate	Mild	64	37
	Total, n (%)		118 (49.0)	102 (42.3)
Poor-responder	Very severe	Very severe	8	25
	Severe	Very severe/severe	9	18
	Moderate	Very severe/severe/moderate	21	20
	Mild	Very severe/severe/moderate	4	4
Total, n (%)			42 (17.4)	67 (27.8)
Undeterminable	Very severe	Severe	8	19
	Severe	Moderate	27	27
	Mild	Mild	46	26
	Total, n (%)		81 (33.6)	72 (29.9)

were still improved in the 2nd season. The proportion of good responders was higher in moderate cases in the 1st season than in severe and very severe cases. However, good responses were also observed in severe or very severe cases in the 1st season. Notably, the comparison between good and poor responder groups showed that TNSMSs of both groups were almost same in the 1st season; however, the mean TNSMS of the good responder group markedly decreased in the 2nd season. Therefore, we cannot predict the efficacy of treatment for the 2nd season based on the severity of symptoms in the 1st season.

The sIgE/tIgE ratio prior to AIT has been found to be significantly higher or lower in good responders compared with poor responders.^{10,20} Fujimura *et al.* reported that a lower ratio could be a predictor of the efficacy of SLIT.¹⁰ However, in the previous phase 3 trial, we reported that the lower ratio was not a predictor of efficacy because the patients with the lower ratio showed lower TNSMSs not only in SLIT group but also in the placebo group.¹¹ In this analysis, there was no significant difference of the ratio between the good and poor responder groups and the ratio also could not predict any efficacy of SLIT.

Previous studies found the allergen-specific IgE as a predictor or biomarker of efficacy of AIT.^{21–23} Previously, we reported that JC pollen-specific IgE increased in the SLIT group early in the treatment but not in the placebo group.¹¹ Furthermore, the increase of the level of JC-specific IgE in serum was lower in the SLIT group in the 2nd season. It is known that allergen-specific IgE level is not constant during the course of a year and increases after the pollen-scattering period. These phenomena would suggest that the suppression of Th2 response is related to the mechanisms of SLIT.

It is generally believed that allergen-specific IgG4 acts as a blocking antibody of mast cells and basophiles and inhibits histamine release.²⁴ However, the relationship between allergen-specific IgG4 and the efficacy of AIT remains controversial. Some reports suggest that allergen-specific IgG4 indicates exposure to the allergen.^{25,26} We have also previously reported that allergen-specific IgG4 increased early after starting SLIT, and the levels remained high in the SLIT group compared with the placebo group.¹¹

Ciprandi *et al.* emphasized that allergen-specific IgE level is an effective predictor of the efficacy of AIT.^{21,22} Di Lorenzo *et al.* also reported the predictive ability of allergen-specific IgE level for SLIT efficacy.²⁰ However, we had the different findings in our analysis presented here. These different findings may be due to a difference between subjects, treatment, or evaluation of symptoms and efficacy; however, the cause is unknown. Schmid *et al.* recently

reported that IgE and IgG4 sensitizations, measured before and after up-dosing SLIT, may be useful for monitoring the early treatment effect.²³ The recent development of molecular allergic examination enables component-resolved diagnosis,²⁷ which can distinguish primary sensitizations from cross-reactivity.²⁸ Although we could not measure the specific IgE against the JC allergen components, it is certain that the increases of JC pollen-specific IgE serum levels indicated an immunologic response to SLIT, based on the comparison between the SLIT group and the placebo group. However, this measure did not appear to be related to the efficacy of SLIT. In the current analysis, the changes in the serum levels of JC pollen-specific IgE and IgG4 were similar in good and poor responder groups, and neither serum immunoglobulin levels were related to the efficacy of SLIT. Many previous reports about biomarkers of SLIT primarily discussed the differences between the SLIT and placebo groups. To evaluate the efficacy of SLIT, the comparison presented here between good and poor responders from within the SLIT group is indispensable.

Many studies have shown that patients with reactivity to multiple allergens account for a large proportion of the allergic population.^{29,30} In this study, we found that 76% of patients were sensitized to allergens other than the JC pollen. Therefore, it is important to determine if SLIT is effective for poly-sensitized patients. In this analysis, SLIT using JC pollen extract was found to be effective for both poly- and mono-sensitized patients. This finding is in agreement with previous reports.^{30–34}

Age is also considered relevant to the efficacy of SLIT. Developed nations, including Japan, are undergoing an aging of the population. In our previous epidemiologic study of the natural history of JC pollen induced AR in middle aged subjects,³⁵ the natural remission rate of the diseases during 10 years was approximately 19%. This result suggests that number of elderly patients with JC pollen induced AR will increase in the future. A previous study determined efficacy and safety of SLIT in elderly subjects.³⁶ In this analysis, age group did not affect the efficacy of SLIT; however, pediatric patients aged <12 years and elderly patients aged >65 years were excluded from this phase 3 trial. Thus, in future studies of the efficacy and safety of SLIT for pediatric and elderly patients should be evaluated.

In conclusion, BMI might modify the effect of SLIT using standardized JC pollen extract (CEDARTOLEN®); however, other factors were not related clearly. The obvious efficacy of SLIT may not be observed until after a certain duration of treatment in many patients. Specifically, the severity of symptoms in the 1st season does not predict that in the 2nd season.

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Conflict of interest

SY, DS received research funding from Torii Pharmaceutical. YO received honoraria for lecture and research funding from Torii Pharmaceutical. KO, MG received honoraria for lecture and writing promotional materials from Torii Pharmaceutical. SK is an employee of Torii Pharmaceutical. AK received honoraria for lecture from Torii Pharmaceutical.

Authors' contributions

SY and YO designed the study and wrote the manuscript. DS checked data and performed the statistical analysis. KO, MG and SK contributed to data collection. AK reviewed the manuscript. All authors concurred with the submission.

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