

An analysis of factors associated with compliance and dropout of sublingual immunotherapy on Japanese cedar pollinosis patients

Takahiro Imanaka, MSc^{1,2}, Izumi Sato, PhD^{1,3}, Yohei Kawasaki, PhD^{1,4}, Yuji Kanazawa, MD, PhD^{1,5} and Koji Kawakami, MD, PhD¹

Background: Sublingual immunotherapy (SLIT) is safe and effective but compliance is problematic. In this study we evaluated dropout and compliance among adults (≥ 20 years of age) and adolescents (< 20 years of age) for Japanese cedar pollen extract (JCPE), an aqueous SLIT approved in 2014 in Japan.

Methods: Administrative claims data on 1236 Japanese patients, 846 adults (mean age, 43.0 years; 41.8% female) and 249 adolescents (mean age, 14.1 years; 36.6% female), with a JCPE prescription between October 2014 and June 2016 were reviewed. Adults and adolescents were divided according to the year they started SLIT (1- and 2-year cohorts) to calculate dropout and compliance and identify associated factors using multivariate Cox and linear regression models.

Results: In 1- and 2-year adult cohorts, dropout rates were 13.5% and 22.1% and compliance rates were 92.8% and 88.8%, respectively. Adolescents had higher dropout and lower compliance. Patients 40-59 years of age had a lower dropout risk than patients 20-29 years of age. Dropout hazard ratios (95% confidence interval) in 1- and 2-year cohorts

were 0.26 (0.12-0.58) and 0.40 (0.17-0.93) in patients 40-49 years of age and 0.32 (0.14-0.75) and 0.35 (0.13-0.92) in patients 50-59 years of age, respectively. Younger age contributed to lower compliance in 1- and 2-year adult cohorts ($p = 0.001$ and $p = 0.02$, respectively). Systemic steroidal medication history and male gender were positively associated with compliance in adults but not in adolescents.

Conclusion: High dropout rate was associated with younger generations. Compliance in adults, but not in adolescents, was associated with age, systemic steroidal medication history, and gender. © 2019 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; dropout; Japanese cedar pollinosis; medication compliance; sublingual immunotherapy

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¹Department of Pharmacoepidemiology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, Japan; ²Research and Development Division, Santen Pharmaceutical Co., Ltd., Ofuka-cho, Kita-ku, Osaka, Japan; ³Keihanshin Consortium for Fostering the Next Generation of Global Leaders in Research, Yoshida-Honmachi, Sakyo-ku Kyoto-shi, Kyoto, Japan; ⁴Biostatistics Section, Clinical Research Center, Chiba University Hospital, Inohana, Chuo-ku, Chiba, Japan; ⁵Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, Japan

Correspondence to: Koji Kawakami, MD, PhD, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; e-mail: kawakami.koji.4e@kyoto-u.ac.jp

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Sublingual immunotherapy (SLIT) is an allergen-specific immunotherapy used to treat a range of environmental allergies and asthma.¹⁻⁴ SLIT has a lower risk of severe adverse events, such as systemic allergic reaction, when compared with subcutaneous immunotherapy (SCIT), thereby allowing more patients to have treatment at home.⁵

In contrast, SLIT can be self-managed whereas SCIT is managed by a physician/health provider. Consequently, SLIT adherence is poorly monitored, resulting in a higher dropout rate and lower compliance compared with SCIT in a real clinical setting.⁶⁻⁹ The rates of dropout within 3 years range between 14% and 93%, but there are major differences in the calculation methods and study designs.⁸⁻¹⁵ Dropout rates appear to be lower in randomized, controlled trials (RCTs) than in observational studies; in one meta-analysis, the RCT composite dropout rate was reported to be 12%.¹⁰

SLIT compliance has also been investigated in observational studies. Reported compliance varied among studies, partly because of differences in calculation methods. In The Netherlands and Spain, compliance rates ranged from around 50% to >90%.^{9,16} Malet et al reported that the proportion of adult patients with good compliance (>80%) was 78.1% over 1 year according to real-world data from Spain.¹⁶

In Japan, the first aqueous SLIT drug, standardized Japanese cedar (JC) pollen extract (Cedartolen®; Torii Pharmaceutical Co., Ltd., Tokyo), was approved and became available on the market in October 2014. Japan adopts a universal healthcare system and standardized JC pollen extract (JCPE) is covered by Japanese health insurance. In Japan, JC pollen is the most common pollinosis-causing antigen, affecting more than 2 million JC pollinosis patients, a number that increases every year.^{17–19} Large JC pollen quantities are scattered far from trees during a brief period each year, most commonly peaking during April.^{19,20} Typically, SLIT is initiated before the JC pollen season.

In an RCT of JCPE treatment conducted in Japan, dropout rates in the first and the second year were reported at 2.4% and 8.7%, respectively.²¹ This dropout rate is low and similar to that reported in a systematic SLIT review, showing approximately 14% patient dropout in the first year.¹⁰ However, such low rates may be different from the real-world situation because observational studies are believed to more accurately reflect the actual clinical situation as compared with RCTs.

Patient dropout and SLIT compliance are affected by factors such as patient characteristics (eg, age), therapy-related factors (eg, effectiveness), and the healthcare environment in each country (eg, hospital visiting frequency, financial burden, insurance coverage).¹⁶ SLIT compliance between adults and children is controversial. Some studies have shown better compliance in adults than in children, but other studies found the opposite.^{8,10,15,16} Typically, children <12 years old have a good compliance, which may be due to the influence of their caregivers, but compliance in adolescents is the same or lower than in adults. It has been reported that adolescents and adults have similar reasons for dropout and low SLIT compliance.^{8–16} Generally, insurance coverage has a strong influence on compliance in the real-world setting.^{22–24} The low dropout and favorable compliance of JCPE in Japan, compared with similar studies in other countries, are therefore likely attributable to its availability to all patients in the Japanese universal health insurance system. However, the JCPE regimen requires use throughout the entire year, including during asymptomatic periods, for at least 3–5 years, which may increase dropout and noncompliance rates. Therefore, actual patient dropout rates and SLIT compliance with JCPE immunotherapy are not clear in the real-world setting.

To develop countermeasures for appropriate SLIT in seasonally allergic patients, it is important to investigate the

actual situation independently of patient health insurance status. Japan is ideal for such a study because of its universal insurance system where patient copayment is constant. Therefore, we investigated SLIT patient dropout and SLIT compliance in a real-world setting using claims data from throughout Japan.

Patients and methods

Study design and data source

This study was a retrospective cohort study conducted using data from the largest commercial claims database in Japan created by Japan Medical Data Center Co., Ltd. (JMDC).²⁵ Since 2005, this database has accumulated more than 3 million individual claims of enrollees and their family members associated with the health insurance of the Japanese universal health care system. Although there is the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), launched by the Japanese government in 2009, it is not commonly used because of the stringent criteria for obtaining access, whereas the JMDC is user-friendly and well-organized. Thus, JMDC has been used for various types of epidemiologic studies.²⁶ The database is sourced from the Japanese union-managed health insurance system and mainly includes salaried workers of medium- to large-scale companies and their dependents. All data were completely anonymized and de-identified. The main elements in the database are patient demographics information, medical claim date, pharmacy claims, and reimbursement cost. Clinical diagnoses present in the database are coded according to *The International Classification of Diseases, 10th Revision* (ICD-10),²⁷ with drug prescription information coded according to the Anatomical Therapeutic Chemical (ATC) classification.²⁸ The data period was from January 1, 2012 to June 30, 2016.

This study was approved by the ethics committee of the Kyoto University School of Medicine (Approval Number R0938). Because all data were anonymized, informed consent of patients was not required based on Japanese ethical guidelines for medical and health research involving human subjects.

Exposure

JCPE is prescribed in 3 dose forms: a 200-U/mL spray bottle; a 2000-U/mL spray bottle; and a 2000-U/mL pack (1 mL), to be taken once a day. JCPE must be prescribed by a suitably trained physician. Patients are treated over 2 phases: an induction phase, with sequentially increased doses administered over a 2-week period, and a maintenance phase. For the 2-week induction phase, a 200-U/mL bottle and a 2000-U/mL bottle are prescribed. Next, the maintenance phase begins, and 2000-U/mL packs are prescribed. Patients take 1 pack (1 mL) once per day during the maintenance phase.

Eligible patients

Patients with data from at least one complete prescription of JCPE (ATC code V01AA05) from October 2014 to June 2016 were considered for the study. Exclusion criteria were the lack of prescription data for the initial 200-U/mL bottle (induction phase) or the initial 2000-U/mL pack (maintenance phase).

Study cohort

All eligible patients were analyzed for age and SLIT initiation date distribution. The analysis of patient dropout and compliance, which was the focus of the study, was performed separately for adults (age, ≥ 20 years) and adolescents (age, < 20 years), because of the reported differences in SLIT compliance between adults and children.^{8–16}

The patients were divided into 3 cohorts according to the initial date of the induction phase: (1) SLIT2014, from October 2014 to April 2015; (2) SLIT2015, from May 2015 to April 2016; and (3) SLIT2016, from May 2016 to June 2016. SLIT2015 (1 year of SLIT) and SLIT2014 (2 years of SLIT) were used for the patient dropout and compliance analysis, whereas SLIT2016 was not used because of the short observation period.

Definition of dropout and SLIT compliance

Dropout was defined as a gap of > 56 days between the last prescription date of the 2000-U/mL pack and the last recorded observation date. This definition was derived from a 2-fold prescription period. Typically, JCPE users should have a monthly visit to the clinical office to obtain the 2000-U/mL pack prescription containing 28 individual units that last for 28 days. We defined the proportion of days covered (PDC) as a surrogate for SLIT compliance, which is the ratio between the number of days that the patient remained in the maintenance phase and the number of 2000-U/mL packs prescribed. The number of days in the maintenance phase was calculated by determining the number of days between the first and the last 2000-U/mL pack prescription date and the number of 2000-U/mL packs prescribed on the last date.

Study outcomes and follow-up

Study outcomes were dropout rate and SLIT compliance during the SLIT treatment phase. These outcomes were observed in each eligible patient from the initiation date of the treatment to June 30, 2016.

Investigated variables

The factors we examined were sex, age, any concurrence of asthma, Charlson Comorbidity Index (CCI), and history of systemic steroid use during cedar pollen season.²⁹ Asthma concurrence was defined as any patient diagnosed with asthma (ICD-10 code J45 and J46) and prescribed inhaled glucocorticoids (ATC code R03BA). Patients were defined as having a history of systemic steroid use if they were prescribed systemic corticosteroids (ATC codes H02A

and H02B) during the JC pollen season before commencing SLIT. The CCI was calculated using ICD-10 codes with associated weighting corresponding to the severity of the comorbid condition of interest. We used patient data starting from January 2012 to calculate these factors.

Statistical methods

Patients' distribution and characteristics

Patient age and date of initiation of the JCPE induction phase were specified and distributions calculated using data from the entire SLIT-eligible cohort (including adults and adolescents). Patient characteristics and investigated variables were described for the adult and adolescent cohorts and each of the selected subgroups (SLIT2014, SLIT2015, and SLIT2016). All variables were assessed using descriptive statistics.

Factors related to dropout

Kaplan-Meier curves of the time to dropout during the maintenance phase were plotted for cohorts associated with variables that were investigated in the study. The mean duration of the maintenance phase and the dropout rate were calculated. To investigate the association between dropout and the investigated variables, univariate and multivariate Cox regression models were developed using each variable (sex, age, concurrence of asthma, CCI, and history of systemic steroid use; age was excluded from the adolescents' analysis). The models were fitted separately using the SLIT2014 and SLIT2015 cohorts to investigate differences in dropout rates during the first year of SLIT (1-year SLIT) and the second year of SLIT (2-year SLIT). Hazard ratio (HR) and 95% confidence interval (CI) were calculated for each variable.

Factors related to SLIT compliance

Mean SLIT compliance was calculated for each cohort. The factors associated with compliance were investigated using linear regression. In this model, the objective variable was SLIT compliance rate, with the explanatory variable adjusted to all investigated variables (sex, age, concurrence of asthma, CCI, and history of systemic steroid use). The standard partial regression coefficient (β'), the regression coefficient (β) with standard error (SE), and 95% CI were calculated for each variable.

SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. A two-sided $p \leq 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 1236 patients were prescribed JCPE during the study period. We excluded 50 patients with no initial data in the induction phase and 91 patients who withdrew from treatment before commencing the maintenance phase

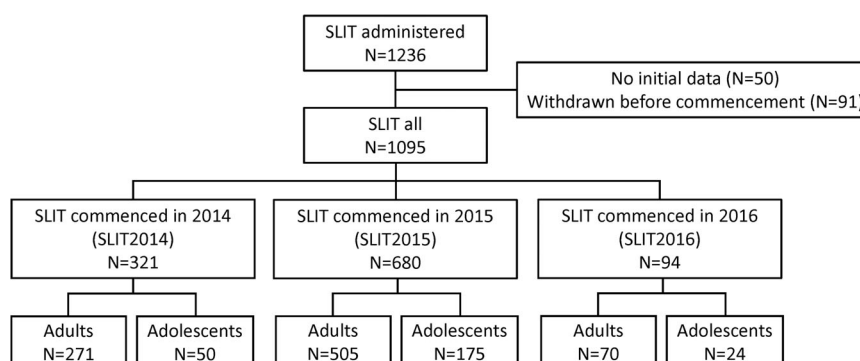


FIGURE 1. Flowchart of the patient selection process.

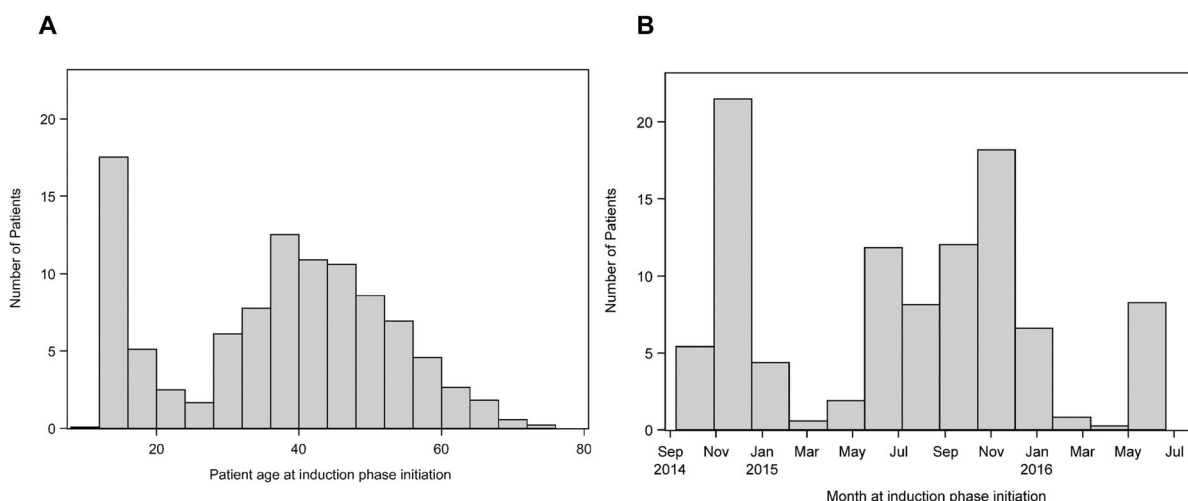


FIGURE 2. Distribution of patients who started the standardized Japanese cedar pollen extract (JCPE) induction phase. (A) Age distribution of JCPE patients selected for the study (SLIT all, 1095 patients). (B) Distribution of the initiation date of the JCPE induction phase (SLIT adults, 846 patients).

(Fig. 1). Patient age at the induction phase showed a bi-modal distribution. The first peak was around 12 years old and the second around 30 years old (Fig. 2A). After excluding some patients, 1095 patients were eligible for the study (Fig. 1). There were 271 adults and 50 adolescents in the SLIT2014 cohort, 505 adults and 175 adolescents in the SLIT2015 cohort, and 70 adults and 24 adolescents in the SLIT2016 cohort. There were no missing data in this study.

Most patients initiated the induction phase after May when JC pollen season was concluding (Fig. 2B). The mean age of eligible adult patients was 43.0 years and 41.8% were female. Most patients were 30-59 years of age. The systemic steroid prescription rate was 34% during the JC pollen season. The proportion of patients with asthma was 3.8% (Table 1). Most of the medical institutions responsible for patient treatment (94.7%) were clinics. These characteristics were similar in each cohort. The mean age of eligible adolescent patients was 14.1 years and 36.6% were female. The mean CCI was 1.4, the systemic steroid prescription rate was 47.8% during the JC pollen season, and the proportion of patients with asthma was 8.4% (Table 2). Adolescents had a lower CCI and a higher proportion of steroid history and asthma complications than adults.

Dropout

In patients in the 1-year SLIT cohort, the mean duration of the maintenance phase and dropout rate were 343.7 days and 13.5%, respectively, whereas, in the 2-year SLIT cohort, these parameters were 501.5 days and 22.1%, respectively. Using multivariate Cox regression models for each age group in the 1-year SLIT cohort (Table 3 and Fig. 3A), hazard ratios (HRs) relative to patients in their 20s were 0.69 (95% CI, 0.34-1.37; $p = 0.29$) for patients in their 30s, 0.26 (95% CI, $p = 0.12$ -0.58; $p = 0.001$) for those in their 40s, 0.32 (95% CI, 0.14-0.75; $p = 0.008$) for patients in their 50s, and 0.18 (95% CI, 0.04-0.82; $p = 0.027$) for patients aged ≥ 60 years of age. Other investigated factors did not show statistically significant relationships with patient dropout. During the 2-year SLIT, HRs relative to patients in their 20s for patients in their 40s and 50s were also statistically significant using multivariate Cox regression models for each age group. The HRs were 0.66 (95% CI, 0.30-1.47; $p = 0.31$) for patients in their 30s, 0.40 (95% CI, 0.17-0.93; $p = 0.03$) for those in their 40s, 0.35 (95% CI, 0.13-0.92; $p = 0.03$) for those in their 50s, and 0.60 (95% CI, 0.19-1.88; $p = 0.38$) for those ≥ 60 years

TABLE 1. Participant demographics and baseline characteristics in the adult population (age, ≥ 20 years)

Characteristics	Adult all (N = 846)	SLIT 2014 (N = 271)	SLIT 2015 (N = 505)	SLIT 2016 (N = 70)
Number of female patients (%)	354 (41.8)	119 (43.9)	201 (39.8)	34 (48.6)
Mean age, in years (SD)	43.0 (10.4)	43.5 (10.2)	43.1 (10.4)	40.9 (10.3)
Number of patents in each age group (%)				
20s	75 (8.9)	21 (7.8)	46 (9.1)	8 (11.4)
30s	259 (30.6)	77 (28.4)	156 (30.9)	26 (37.1)
40s	279 (33.0)	98 (36.2)	160 (31.7)	21 (30.0)
50s	176 (20.8)	54 (19.9)	111 (22.0)	11 (15.7)
≥ 60	57 (6.7)	21 (7.8)	32 (6.3)	4 (5.7)
CCI (median)	2.5 (2.0)	2.5 (2.0)	2.6 (2.0)	2.1 (2.0)
Systemic steroid history (%)	321 (37.9)	92 (34.0)	199 (39.4)	30 (42.9)
Asthma (%)	32 (3.8)	9 (3.3)	21 (4.2)	2 (2.9)
Management body [number of patients (%)]				
Clinic	772 (94.7)	241 (94.9)	465 (94.5)	66 (95.7)
University hospital	15 (1.8)	5 (2.0)	9 (1.8)	1 (1.5)
Public hospital	4 (0.5)	2 (0.8)	2 (0.4)	0 (0.0)

CCI = Charlson Comorbidity Index; SD = standard deviation.

TABLE 2. Participant demographics and baseline characteristics in the adolescent population (age, < 20 years)

Characteristics	Adolescent all (N = 249)	SLIT 2014 (N = 50)	SLIT 2015 (N = 175)	SLIT 2016 (N = 24)
Number of female patients (%)	91 (36.6)	11 (22.0)	70 (40.0)	10 (41.7)
Mean age in years (SD)	14.1 (1.9)	14.1 (2.1)	14.1 (1.9)	13.9 (2.0)
CCI (median)	1.4 (1.2)	1.6 (1.3)	1.4 (1.1)	1.0 (1.0)
Systemic steroid history (%)	119 (47.8)	16 (32.0)	87 (49.7)	16 (66.7)
Asthma (%)	21 (8.4)	3 (6.0)	16 (9.1)	2 (8.3)
Management body [number of patients (%)]				
Clinic	220 (90.9)	41 (89.1)	155 (90.1)	24 (100.0)
Public hospital	10 (4.1)	1 (2.2)	9 (5.2)	0 (0.0)
Other	12 (5.0)	4 (8.7)	8 (4.7)	0 (0.0)

CCI = Charlson Comorbidity Index; SD = standard deviation.

of age. In contrast to the 1-year SLIT cohort, the HRs for patients ≥ 60 years old were not statistically significant. Systemic steroid history showed statistically low HRs in univariate analysis but no statistical significance in multivariate analysis (Table 3 and Fig. 3B).

SLIT compliance

SLIT compliance in adults was 92.8% in all patients in the 1-year SLIT cohort and 88.8% in the 2-year SLIT cohort. For the 1-year cohort, age was the only statistically significant factor associated with compliance ($p = 0.001$) (Table 4). In this model, increasing age was associated with

a higher rate of SLIT compliance during 1 year of SLIT. In the 2-year SLIT cohort, sex, age, and systemic steroid history were statistically significant factors associated with compliance ($p = 0.03$, 0.02 , and 0.04 , respectively) (Table 4). Compliance increased in males with age and having a systemic steroid history increased compliance during 2 years of SLIT.

Dropout and SLIT compliance in adolescents

In adolescents in the 1-year SLIT, the mean duration of the maintenance phase and dropout rate were 284.7 days and 22.3%, respectively, whereas, in the 2-year SLIT, these

TABLE 3. Risk factors associated with dropout during the 1- and 2-year SLIT maintenance period

Factors	1-year SLIT (SLIT2015)						2-year SLIT (SLIT2014)					
	Number of patients	% of dropouts	Univariate analysis			p value	Number of patients	% of dropouts	Univariate analysis		p value	Multivariate analysis
			HR (95% CI)	p value	HR (95% CI)				HR (95% CI)	p value		HR (95% CI)
All	505	13.5					271	22.1				
Sex												
Male	304	12.8	1		1		152	26.3	1			1
Female	201	14.4	1.16 (0.72-1.88)	0.54	1.23 (0.75-2.01)	0.42	119	16.8	0.59 (0.34-1.00)	0.052	0.64 (0.37-1.12)	0.12
Age	505	13.5	0.96 (0.93-0.98)	0.0003	–	–	271	22.1	0.96 (0.94-0.99)	0.0068	–	–
Age group												
20s	46	23.9	1		1		21	42.9	1			1
30s	156	19.2	0.70 (0.35-1.40)	0.31	0.69 (0.34-1.37)	0.29	77	27.3	0.62 (0.28-1.35)	0.23	0.66 (0.30-1.47)	0.31
40s	160	8.8	0.29 (0.13-0.65)	0.0025	0.26 (0.12-0.58)	0.001	98	17.4	0.35 (0.16-0.78)	0.01	0.40 (0.17-0.93)	0.03
50s	111	9.9	0.35 (0.15-0.80)	0.013	0.32 (0.14-0.75)	0.008	54	14.8	0.31 (0.12-0.80)	0.02	0.35 (0.13-0.92)	0.03
≥60 years	32	6.3	0.21 (0.05-0.94)	0.041	0.18 (0.04-0.82)	0.027	21	23.8	0.59 (0.20-1.78)	0.35	0.60 (0.19-1.88)	0.38
CCI												
<2.0	193	13.5	1		1		102	25.5	1			1
≥2.0	312	13.5	1.00 (0.61-1.63)	0.99	1.27 (0.76-2.12)	0.37	169	20.1	0.75 (0.45-1.26)	0.28	0.97 (0.56-1.68)	0.90
Systemic steroid history												
No	306	11.8	1		1		179	26.3	1			1
Yes	199	16.1	1.42 (0.88-2.29)	0.15	1.49 (0.92-2.42)	0.10	92	14.1	0.50 (0.27-0.92)	0.02	0.55 (0.29-1.02)	0.056
Asthma												
No	484	13.6	1		1		262	22.1	1			1
Yes	21	9.5	0.64 (0.16-2.63)	0.54	0.65 (0.16-2.70)	0.55	9	22.2	1.04 (0.25-4.25)	0.96	1.16 (0.27-4.90)	0.84

CCI = Charlson Comorbidity Index; CI = confidence interval; HR = hazard ratio; SLIT = sublingual immunotherapy.

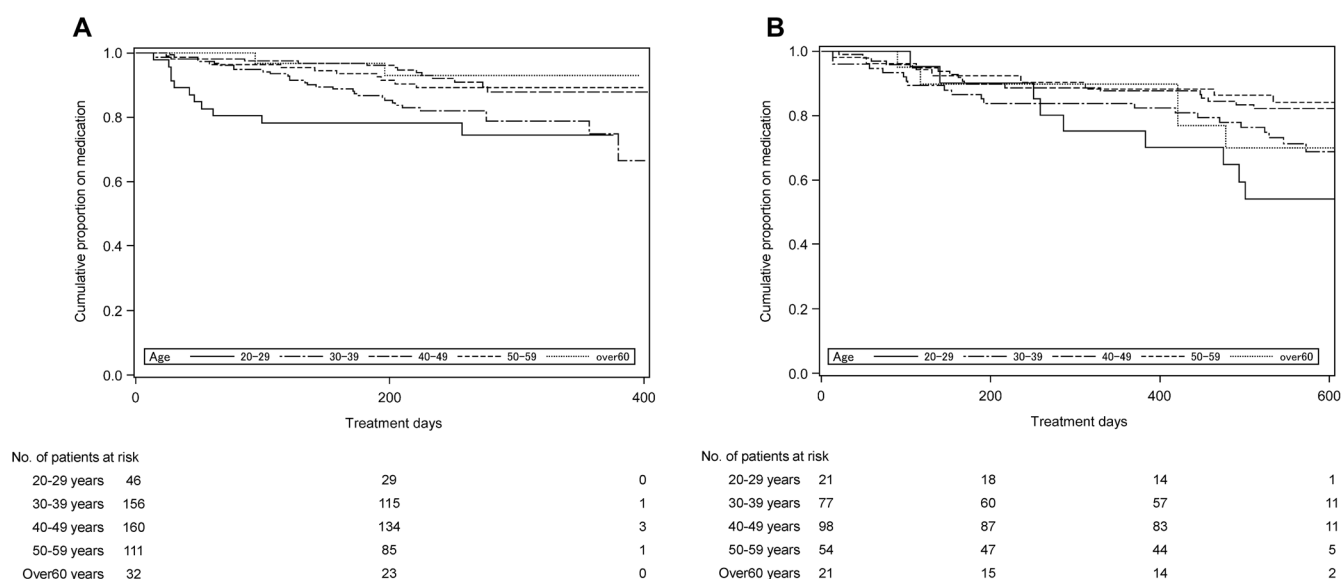


FIGURE 3. Kaplan-Meier curves of the time to dropout during the maintenance phase with age groups for the 1-year SLIT cohort (A) and the 2-year SLIT cohort (B).

TABLE 4. Risk factors associated with compliance during maintenance period

Factors	1-year SLIT (SLIT2015)				2-year SLIT (SLIT2014)			
	β'	β	SE (95% CI)	p value	β'	β	SE (95% CI)	p value
Intercept	0	84.39	2.44 (79.59–89.18)	<0.0001	0	77.09	6.31 (64.67–89.51)	<0.0001
Sex (female)	0.01	0.26	1.15 (–2 to 2.52)	0.82	–0.14	–6.6	2.93 (–12.37 to –0.82)	0.03
Age	0.15	0.19	0.06 (0.08–0.3)	0.001	0.15	0.35	0.15 (0.06–0.64)	0.02
CCI	0.01	0.06	0.26 (–0.46 to 0.58)	0.82	–0.09	–1.09	0.74 (–2.54 to 0.36)	0.14
Systemic steroid history	0.01	0.26	1.16 (–2.01 to 2.53)	0.82	0.12	6.2	3.07 (0.16–12.24)	0.04
Asthma	0.02	1.43	2.82 (–4.12 to 6.98)	0.61	0.02	2.01	8.07 (–13.88 to 17.91)	0.8

β = regression coefficient; β' = standard partial regression coefficient; CCI = Charlson Comorbidity Index; CI = confidence interval; SE = standard error; SLIT = sublingual immunotherapy.

parameters were 493.0 days and 36.0%, respectively. Univariate and multivariate Cox regression analysis did not identify a statistically significant association between patient dropout and any of the monitored parameters. SLIT compliance was 90.5% in the 1-year SLIT cohort and 85.1% in the 2-year SLIT cohort. There were no statistically significant factors associated with compliance.

Discussion

In this study, we have investigated patient dropout and SLIT compliance in a retrospective cohort study of SLIT by JCPE for the treatment of JC pollinosis. The goal of the study was to determine contributing factors in a real-world clinical setting. Dropout rates lower than those previously reported, as well as high compliance, were observed. Patient age, systemic steroid use history, and sex were factors associated with low dropout rates and high SLIT compliance.

In the 1-year SLIT cohort of adults, dropout rate and mean SLIT compliance were 13.5% and 92.8%, respectively, whereas, in the 2-year SLIT cohort, the dropout rate was 22.1% and the mean SLIT compliance 88.8%. The dropout rates are lower and the SLIT compliance rates are higher than those reported in previous studies from other countries.^{8,9,14–16} The major determinants associated with high dropout rates and low compliance during SLIT are known to be lack of efficacy, patient's perception of efficacy, cost of treatment, and convenience of administration.^{16,30} In addition, the convenience of access to treatment was reported as one of the positive factors for a low dropout rate of SLIT.⁹ Therefore, a major reason for the low dropout rates in Japan may be the accessibility of clinics and/or the low medical costs for patients in a universal health insurance system.

Patient age was associated with SLIT dropout in adults, and the dropout rates in adolescents were higher than those in adults. Young adult patients (<30 years of age) were

found to be more likely to drop out of the JCPE SLIT regimen. Dropout rates among patients in their 40s and 50s were relatively low compared with the rates for those in their 20s. This may be associated with lower average income and higher likelihood of undergoing changes in location (and therefore changes in attending physician) by patients in their 20s compared with those in their 40s or 50s. As in the case of dropouts, lower average income may be a major reason for low compliance because the compliance rate is related to patient age and was seen to improve with age in the first year. The dropout hazard rate in patients aged ≥ 60 years was lower than that of patients in their 20s in the first year, but there was no difference in the second year. As the SLIT duration became longer, elderly patients may have had problems due to medication cost or a less stable housing situation, like patients in their 20s, or they may have been more likely to consider that the medication lacked efficacy. In this study, dropout rates were higher in adolescents than in adults. Although previous studies reported differences in SLIT compliance between adults and children, the results in children have been inconsistent.^{8–16} High compliance was observed in children <12 years of age, which may be due to the dose management by caregivers. It is also possible that frequent check-ups with a specialist during the short periods led to better compliance.⁸ However, adolescents of ≥ 15 years of age had high dropout rates because of the complexity of SLIT and the long treatment period. The same reasons were reported for adults.¹⁶ In this study, we found low compliance in pediatric patients, most of them ≥ 12 years of age. Our results with adolescent compliance were similar to those of previous studies.^{8,16} In Japan, adolescents between 12 and 20 years of age undergo a drastic changes in their environment within a short period due to advancements in their education level every 3 years by proceeding through junior high school, high school, and university. This environment could make it difficult to continue SLIT.

Interestingly, systemic steroid history improved SLIT compliance in the second year in adults, indicating that patients with more severe allergic rhinitis have better compliance even with long-term treatment because systemic steroid treatment is only used in severe cases according to the Japanese guideline for allergic rhinitis.³¹ Thus, patients with severe disease may tend to continue SLIT. Indeed,

more patients with severe symptoms are selected for SLIT than other therapies.^{32,33} However, steroid history was not associated with SLIT compliance in adolescent patients. This difference may depend on the patient's background, such as increased steroid-use history in adolescents. Further studies are needed to assess the efficacy of SLIT in more severe cases.

The strength of our study is that it was based on real-world data. Accordingly, the results are a better reflection of the actual situation than RCTs or other prospective study designs. Furthermore, because the JMDC database is sourced from a union-managed health insurance system, we were able to identify all insurance-covered medical records for each patient, even if they visited multiple hospitals and/or changed their health-care provider. Therefore, we were able to evaluate the dropouts using all insurance-covered medical records in the JMDC database.

There are 4 major limitations to this study. First, the JMDC data were taken from the employed population, so the representation of patients aged ≥ 65 years of age was low compared with the general Japanese population. However, JC pollinosis is not an age-related disease, so the influence of this limitation on our findings may have been very small. Second, because the JMDC database does not include addresses of the patients, we could not take into consideration the extent of scattering of the cedar pollen, which could vary between the home addresses of patients in the cohort. Third, we may have underestimated dropout rates and SLIT compliance. We could not directly measure the SLIT compliance even if the prescription was regularly recorded. Finally, there may have been other, yet unknown factors that influence dropout or compliance.

Conclusion

We identified a low dropout rate and high compliance of SLIT compared with previous reports from other countries. Systemic steroid use is associated with better compliance, suggesting that SLIT may be effective even in patients with severe disease. Age was a factor related to both dropout and compliance; younger patients tended to have high dropout rates and low compliance. Further studies are needed to elucidate the reasons for the strong influence of age on dropout and compliance so we may take steps that will lead to improved SLIT efficacy. 

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