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SUPPORTING INFORMATION

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Real-world compliance and determinants for sublingual allergen immunotherapy in children and parents

To the Editor,

Allergic rhinitis (AR) is a global public health issue, including Japan.[1,2] The burden of AR is substantial because AR was associated with controlling asthma, lower quality of life, decreased school and work performance, elevated direct healthcare costs, and indirect costs due to lost work productivity.[3] Sublingual allergen immunotherapy (SLIT), an established treatment for AR, requires a high level of compliance for at least 3 years to achieve the desired disease-modifying effects.[4] However, compliance and its determinants for children and parents remain unknown at nationwide levels.

We conducted a retrospective cohort study to identify compliance with SLITs and to explore factors associated with high compliance among children and parents during 2015–2021 using the database provided by the Japan Medical Data Center and DeSC Healthcare Inc. This study received approval from our institutional review board (#2022-176). The details of these databases have been described in Table S1.

We extracted all data on all children aged <20 years and their parents, and then included data on individuals who received SLITs for Japanese cedar pollen (Cedarcure®) or for house dust mites of *Dermatophagoides farina* and *Dermatophagoides pteronyssinus* (Miticure®, Actair®; Table S1). We followed them for 3 years or right-censoring. Consequently, our study used data from 49,159 individuals, amounting to 919,398 person-months. Patient variables included age, AR treatment, comorbid allergic diseases, and family members undergoing SLIT. Compliance rates were defined by days of therapies for SLIT as the numerator and 100 person-days as the denominator and reported as DOTs/100PDs (Supplementary Method).[5]

The data analyses included five steps using Stata/MP software version 18.1. Firstly, we summarized baseline characteristics (Table S2). Secondly, we investigated the trends in compliance rates using multivariable Poisson regression models under cluster robust variance. Thirdly, we explored factors associated with high compliance (>75 DOTs/100PDs). Fourthly, we presented the Sanky

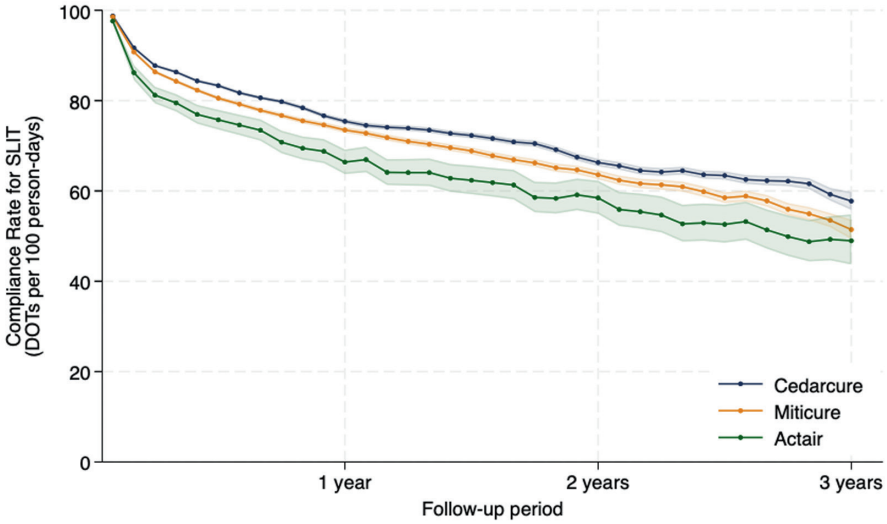

FIGURE 1 Compliance rates as days of therapy per 100 person-days (DOTs/100 PDs).

diagram for the flow of compliance status. Fifth, we conducted a series of sensitivity analyses.

The compliance rates for Cedarcure®, Miticure®, and Actair® decreased from 98.7, 98.5, and 97.6 DOTs/100 PDs in the first month to 57.8, 51.4, and 48.9 DOTs/100PDs in the 36th month, respectively (Figure 1). Factors associated with high compliance were Cedacure®, younger children, male, AR treatment, atopic dermatitis/eczema, and summer initiation for patient characteristics, and public/university hospitals and otolaryngology/pediatrics departments for hospital characteristics (Table 1). Proportions of individuals with high compliance dropped from 75.6% during the 1st year to 53.9% during the 3rd year (Figure S1).

For sensitivity analyses, we firstly stratified data by age categories and investigated the role of family members. The presence of offspring with SLITs was associated with high compliance among parents aged 20–39 years (Table S3). Secondly, among all age groups, the highest compliance rates were observed in the Cedacure® group (Figure S2). Thirdly, the Sanky diagrams for age-specific categories were presented in Figure S3.

Our study found relatively low compliance rates with variations by life stages: younger children were the most compliant, whereas adolescents were the least compliant. Having children undergoing SLIT can boost compliance rates among younger parents, probably because parents of younger children with SLITs could feel a heightened sense of responsibility to strictly adhere to their treatment regimen. The highest compliance rates were observed in the Cedarcure® group, followed by the Miticure® and Actair® groups, partially attributed by the likelihood for adverse reactions (Table S1). Our study has several limitations; misclassification of diagnosis, the lack of clinical information, and unclear generalizability of our findings to the entire population in Japan.

In conclusion, our study provides novel insights into the compliance rates for SLITs and their determinants. These findings may be utilized to improve the compliance of SLIT among children and parents.

TABLE 1 Factors associated with high compliance for sublingual immunotherapy (SLIT).

Measurement	High compliance defined by >75 DOTs/100 PDs	
Effect estimates	Risk ratio	(95% Confidence interval)
Treatment		
Cedarcure®	Reference	
Miticure®	1.008	(0.996, 1.020)
Actair®	0.956	(0.917, 0.997)
Age category		
<10 years	Reference	
10–19 years	0.846	(0.835, 0.857)
20–39 years	0.840	(0.817, 0.863)
40 years or older	0.937	(0.917, 0.957)
Sex		
Female	Reference	
Male	1.014	(1.002, 1.026)
Treatment history for allergic rhinitis		
Oral antihistamine	1.102	(1.083, 1.122)
Nasal steroid spray	1.024	(1.009, 1.039)
Ophthalmic steroid or antihistamine	1.067	(1.050, 1.084)
Comorbid diseases		
Asthma	0.995	(0.982, 1.008)
Atopic dermatitis/Eczema	1.034	(1.021, 1.049)
Food allergy	0.980	(0.958, 1.001)
Family member undergoing SLIT	1.011	(0.998, 1.023)
Medical facility types		
Clinic	Reference	
Public hospital	1.146	(1.098, 1.197)
University hospital	1.180	(1.129, 1.234)
Others	1.150	(1.101, 1.201)

TABLE 1 (Continued)

Measurement	High compliance defined by >75 DOTs/100 PDs	
Effect estimates	Risk ratio	(95% Confidence interval)
Clinical department		
Otolaryngology	Reference	
Pediatrics	1.002	(0.989, 1.017)
Internal medicine	0.943	(0.925, 0.960)
Others	0.914	(0.885, 0.944)
Month for initial treatment		
January	Reference	
February	0.993	(0.949, 1.038)
March	1.006	(0.966, 1.047)
April	1.051	(1.010, 1.093)
May	1.086	(1.050, 1.124)
June	1.106	(1.070, 1.143)
July	1.093	(1.057, 1.131)
August	1.076	(1.041, 1.113)
September	1.072	(1.035, 1.110)
October	1.062	(1.026, 1.099)
November	1.051	(1.015, 1.089)
December	1.042	(1.003, 1.081)

Abbreviation: DOTs/100 PDs, days of therapy per 100 person-days.

AUTHOR CONTRIBUTIONS

Drs. Okubo coordinated the data management, drafted the initial manuscript, and performed the initial analyses. Drs. Kuwabara, Sato, Sakashita, Hayashi, and Morita supervised the study design, revised the manuscript, and approved the final manuscript as submitted. Each author has seen and approved the submission of the manuscript and takes full responsibility for its contents.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

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