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Clinical practice pattern of *Pneumocystis* pneumonia prophylaxis in systemic lupus erythematosus: a cross-sectional study from lupus registry of nationwide institutions (LUNA)

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Abstract

Background *Pneumocystis jirovecii* pneumonia (PCP) is an opportunistic infection in patients undergoing immunosuppressive therapy, such as glucocorticoid (GC) medication, for systemic autoimmune diseases like systemic lupus erythematosus (SLE). Despite the confirmed effectiveness of PCP prophylaxis, its clinical administration, especially in conjunction with GC dosage, remains unclear. We aimed to describe the clinical practice of PCP prophylaxis in association with SLE in Japan, evaluate the relationship between GC dosage and PCP prophylaxis, and explore the practice patterns associated with PCP prophylaxis.

Methods This cross-sectional study used data from the Lupus Registry of Nationwide Institutions in Japan from 2016 to 2021 and included patients diagnosed with SLE. Using descriptive statistics, multivariate analysis, and decision tree analysis, we examined the prevalence of PCP prophylaxis and its association with the GC dosage.

Results Out of 1,460 patients, 21% underwent PCP prophylaxis. The frequency of prophylaxis decreased with a decrease in GC dosage. After adjusting for confounders, logistic regression revealed the odds ratio of PCP prophylaxis increased with higher prednisolone (PSL) doses: 3.7 for $5 \leq PSL < 7.5$ mg, 5.2 for $7.5 \leq PSL < 10$ mg, 9.0 for $10 \leq PSL < 20$ mg, and 43.1 for $PSL \geq 20$ mg, using $PSL < 5$ mg as the reference. Decision tree analysis indicated that a PSL dosage of < 11 mg/day and immunosuppressant use were key determinants of PCP prophylaxis.

Conclusion This study provides valuable insights into PCP prophylaxis practices in patients with SLE in Japan, underscoring the importance of GC dosage and concomitant immunosuppressant use.

Keywords Systemic lupus erythematosus, *Pneumocystis jirovecii* pneumonia, Glucocorticoid, Immunosuppressant, Practice pattern

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Background

Pneumocystis jirovecii pneumonia (PCP) is a severe infection that often develops in patients with suppressed immune systems, such as those receiving immunosuppressive treatment for systemic autoimmune diseases [1]. Patients undergoing immunosuppressive therapy who develop PCP are directly linked to a poor prognosis; however, prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) administration is extremely effective in preventing the onset of PCP [2, 3]. A previous meta-analysis reported an 85% reduction in the incidence of PCP in patients receiving prophylaxis with TMP/SMX [4].

Various risk factors for the development of PCP have been reported, among which glucocorticoids (GCs) are known to pose a dose-dependent risk of PCP [5, 6]. However, it remains unclear whether prophylaxis should be discontinued in patients receiving GCs. Even in patients with systemic lupus erythematosus (SLE), a typical autoimmune disease, GCs remain the mainstay of treatment [7]. GC dosage, disease activity, renal involvement, and lymphocyte count have been reported as risk factors for PCP in patients with SLE [8], suggesting that prophylaxis may be necessary in certain patients. On the other hand, the frequency of adverse events due to TMP/SMX has been reported to be higher in patients with SLE [9], implying that prophylaxis is not being administered. However, the actual clinical practice of PCP prophylaxis in Japan is not clear.

We aimed to 1) describe the clinical practice of PCP prophylaxis in association with SLE in Japan, 2) evaluate the relationship between GC dosage and PCP prophylaxis, and 3) explore the practice patterns associated with PCP prophylaxis to help determine the optimal timing for discontinuing PCP prophylaxis administration.

Methods

Study design and setting

This cross-sectional study used data acquired through a multidisciplinary cohort study (the Lupus Registry of Nationwide Institutions [LUNA]) conducted in 2016 to investigate the association between clinical manifestations, socioeconomic backgrounds, and outcomes of patients with SLE reported from 14 Japanese institutions. Approximately 2.3% of patients with SLE in Japan have been registered in the LUNA, accounting for approximately 1,500 cases.

Patient selection and outcome measure

The study population comprised patients aged 20 years or older, diagnosed according to the revised 1997 American College of Rheumatology (ACR) criteria for SLE classification [10].

This study was performed using electronic medical records and self-administered questionnaires completed by patients registered from January 2016 to January 2021. All the data were collected at the time of registration. The primary outcome was the proportion of patients who underwent PCP prophylaxis, which was defined as the administration of TMP/SMX, pentamidine, or atovaquone.

Collected variables

Besides PCP prophylaxis, we collected the following data: age, sex, disease duration, GC dosage (current and past maximum, prednisolone [PSL] equivalent), hydroxychloroquine use, immunosuppressant use, biologics use, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) [11], Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) [12], white blood cell (WBC) count, lymphocyte count, anti-double stranded DNA antibody level, complement (C3, C4, CH50) level, serum creatinine level, and immunoglobulin (Ig) G levels.

Statistical analysis

The descriptive statistics of the enrolled patients were expressed as median and interquartile range (IQR) for continuous variables and as n (%) for categorical variables. First, we determined the proportion of patients who received PCP prophylaxis. We compared the characteristics of patients who received PCP prophylaxis at registration with those of patients who did not. Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the chi-square test or Fisher's direct probability test, as appropriate. We used multiple imputations to handle the uncertainty caused by missing values, assuming that they were missing at random. For the comparisons among GC dose groups, stratification was performed as follows: Group 1 was defined as "PSL < 5 mg," Group 2 as "5 mg ≤ PSL < 7.5 mg," Group 3 as "7.5 mg ≤ PSL < 10 mg," and Group 4 as "≥ 10 mg." The association between the actual prescription of PCP prophylaxis and GC dosage was evaluated via univariate and multivariate logistic regression analysis, with the adjustment for confounding factors selected based on previous reports. Finally, decision tree analysis using the classification and regression tree (CART) algorithm was performed to search for practice patterns related to PCP prophylaxis. The procedures were conducted using R-package "rpart" (https://cran.r-project.org/web/packages/rpart/rpart.pdf). This machine learning method is an exploratory and data-driven analysis

that recursively splits data into subsets based on a target variable, in this study PCP prescription. The CART algorithm uses Gini impurity for categorical variables and mean square error for continuous variables to create as homogeneous a subset as possible with respect to PCP prescriptions, that leads to identify and visualize which of the various factors are associated with PCP prescriptions and, for continuous variables, what the cutoff is. The candidate variables included in the model were age (continuous), sex (categorical), GC dosage (continuous), hydroxychloroquine use (categorical), immunosuppressant use (categorical), biologic use (categorical), SLEDAI-2 K (continuous), lymphocyte count (continuous), and IgG levels (continuous). The tree size was determined to minimize the cross-validation error. The maximum tree depth was set at 30 cases, the smallest parent node at 15, and the smallest child node at 5.

Statistical significance was set at $p < 0.05$. The statistical analyses were performed using the Statistical Package of Stata, version 17.0 (StataCorp, College Station, TX, USA) unless otherwise specified.

Patient and public involvement

Neither the general public nor the patients with SLE were involved in the planning, recruitment, or conduct of this study.

Results

Enrolled patient characteristics

Of the 1,541 patients registered in the LUNA, 62, 15, and 4 patients were excluded because of a lack of information about age/sex, PCP prophylaxis, and current pregnancy, respectively. The median (IQR) age of the enrolled 1,460 patients was 46 (36 to 58) years, and 1,279 (88%) patients were female. The median (IQR) disease duration was 13 (6 to 21) years. The median (IQR) SLEDAI and total SLICC-DI scores at registration were 4 (2 to 8) and 1 (1 to 2), respectively. Immunosuppressants and hydroxychloroquine were used in 888 (61%) and 462 (32%) patients, respectively (Table 1).

PCP prophylaxis and GC treatment status

PCP prophylaxis was performed in 293 patients (21%), and the medications included TMP/SMX in

Table 1 Comparison of characteristics between patients with and without *pneumocystis* pneumonia prophylaxis

Characteristics	Total ($n = 1,460$)	Without prophylaxis ($n = 1,167$)	Number of Missing data	With prophylaxis ($n = 293$)	Number of Missing data	*p*-value
Trimethoprim/sulfamethoxazole	266	-	-	266		
Pentamidine	4	-	-	4		
Atovaquone	23	-	-	23		
Age, years	46 (36 to 58)	46 (37 to 59)	0	43 (30 to 55)	0	< 0.001
Female patients, n (%)	1,279 (88)	1,035 (89)	0	244 (83)	0	0.012
Disease duration, years	13 (6 to 21)	14 (7 to 23)	24	7 (3 to 16)	4	< 0.001
SLEDAI-2 K	4 (2 to 7)	4 (2 to 6)	1	4 (2 to 8)	0	< 0.001
SLICC-DI	1 (1 to 2)	1 (1 to 2)	0	1 (1 to 2)	0	0.17
Maximum PSL dosage after diagnosis, mg/day	40 (30 to 54)	40 (25 to 50)	127	50 (40 to 60)	13	< 0.001
Current PSL dosage, mg/day	5.0 (4.0 to 9.0)	5.0 (3.0 to 7.5)	4	9.0 (5.5 to 15.0)	1	< 0.001
Current immunosuppressant use	888 (61)	645 (55)	1	243 (83)	0	< 0.001
Current hydroxychloroquine use	462 (32)	344 (30)	5	118 (40)	0	< 0.001
Current biologics use	40 (4)	25 (3)	299	15 (7)	67	0.004
White blood cells, /μL	5640 (4300 to 7400)	5550 (4300 to 7265)	3	6200 (4300 to 7800)	0	0.024
Lymphocyte, /μL	1050 (690 to 1475)	1082 (741 to 1493)	37	896 (581 to 1318)	16	< 0.001
Lymphocyte < 500/μL	151 (11)	102 (9)	37	49 (18)	16	< 0.001
C3, mg/dL	81.0 (68.4 to 95.0)	82.0 (69.1 to 96.0)	189	78.0 (67.0 to 91.0)	32	0.004
C4, mg/dL	16.0 (11.1 to 21.9)	16.1 (11.3 to 21.9)	234	15.0 (10.0 to 21.8)	62	0.12
CH50, U/mL	37.6 (30.0 to 46.1)	37.3 (30.5 to 46.0)	165	38.3 (28.1 to 47.0)	51	0.97
Anti-ds-DNA-antibody, EU/mL	7.3 (2.0 to 17.2)	7.2 (1.9 to 16.8)	250	7.6 (2.5 to 21.4)	41	0.13
Serum creatinine, mg/dL	0.7 (0.6 to 0.8)	0.7 (0.6 to 0.8)	19	0.7 (0.6 to 0.9)	3	0.022
IgG, mg/dL	1309 (1046 to 1643)	1353 (1092 to 1677)	339	1129 (888 to 1461)	79	< 0.001
IgG < 500 mg/dL	10 (1.0)	5 (0.6)	339	5 (2.3)	79	0.020

Continuous variables were reported as medians with interquartile ranges, while categorical variables were presented as counts and percentages (n, %)

PSL prednisolone, *SLEDAI-2 K* Systemic Lupus Erythematosus Disease Activity index 2000, *SLICC-DI* systemic lupus international collaborative clinics damage index

266 patients, atovaquone in 23, and pentamidine in 4 (Table 1). The characteristics of patients who underwent and who did not undergo PCP prophylaxis are shown in Table 1. The former were younger; more likely to be male; had a shorter disease duration; higher SLEDAI; higher previous maximum dosage of PSL; use of immunosuppressive drugs, hydroxychloroquine, and biological agents; higher WBC count; lower lymphocyte count; lower C3 levels; higher serum creatinine levels; and lower IgG levels than did those without PCP prophylaxis.

Table 2 Univariate and multivariate logistic regression analysis of association of *pneumocystis* pneumonia prophylaxis and daily glucocorticoid dosage, after multiple imputations of missing values

	Crude OR (95%CI)	Adjusted[a] OR (95%CI)
PSL < 5 mg/day	Reference	Reference
5 ≤ PSL < 7.5 mg/day	4.4 (2.7 to 7.2)	3.7 (2.2 to 6.1)
7.5 ≤ PSL < 10 mg/day	7.3 (4.2 to 12.6)	5.2 (3.0 to 9.3)
10 ≤ PSL < 20 mg/day	11.5 (6.9 to 19.3)	9.0 (5.3 to 15.5)
PSL ≥ 20 mg/day	44.7 (23.3 to 85.8)	43.1 (21.3 to 87.2)

CI confidence interval, *OR* odds ratio

[a] Adjusted for age, sex, Systemic Lupus Erythematosus Disease Activity Index 2000, systemic lupus international collaborative clinics damage index, hydroxychloroquine use, immunosuppressant use, and biologics use

The GC dosages at registration were stratified as follows: Group 1(PSL < 5 mg/day) in 454 (31%), Group 2 (5 ≤ PSL < 7.5 mg/day) in 519 (36%), Group 3 (7.5 ≤ PSL < 10 mg/day) in 180 (12%), and Group 4 (10 ≤ PSL < 20 mg/day) in 226 (16%), and Group 5 (PSL ≥ 20 mg/day) in 76 (5%) patients. In 5 cases, information about GS dosages was lacking. The proportion of the patients who underwent PCP prophylaxis decreased with decreasing GC dosage: Group 5 (PSL ≥ 20 mg), 52/76 (68%); Group 4 (10 ≤ PSL < 20 mg), 81/226 (36%); Group 3 (7.5 ≤ PSL < 10 mg,) 47/180 (26%); Group 3 (5 ≤ PSL < 7.5 mg), 91/519 (18%); and Group 4 (< 5 mg), 21/454 (5%).

After adjusting for age, sex, hydroxychloroquine use, immunosuppressant use, biologics use, SLEDAI, and SLICC-DI as confounders, logistic regression analysis showed that the odds ratios for PCP prophylaxis were 3.7 (95% confidence interval [CI], 2.2 to 6.1) in Group 2 (5 ≤ PSL < 7.5 mg), 5.2 (95% CI, 3.0 to 9.3) in Group 3 (7.5 ≤ PSL < 10 mg), 9.0 (95% CI, 5.3 to 15.5) in Group 4 (10 ≤ PSL < 20 mg), and 43.1 (95% CI, 21.3 to 87.2) in Group 5 (PSL ≥ 20 mg) when Group 1 (PSL < 5 mg) was used as the reference group (Table 2).

Decision tree analysis related to the PCP prophylaxis

Figure 1 shows the results of the decision tree analysis. PSL dosage and immunosuppressant use were identified as important variables associated with PCP prophylaxis (Supplemental Table 1). The CART algorithm split the

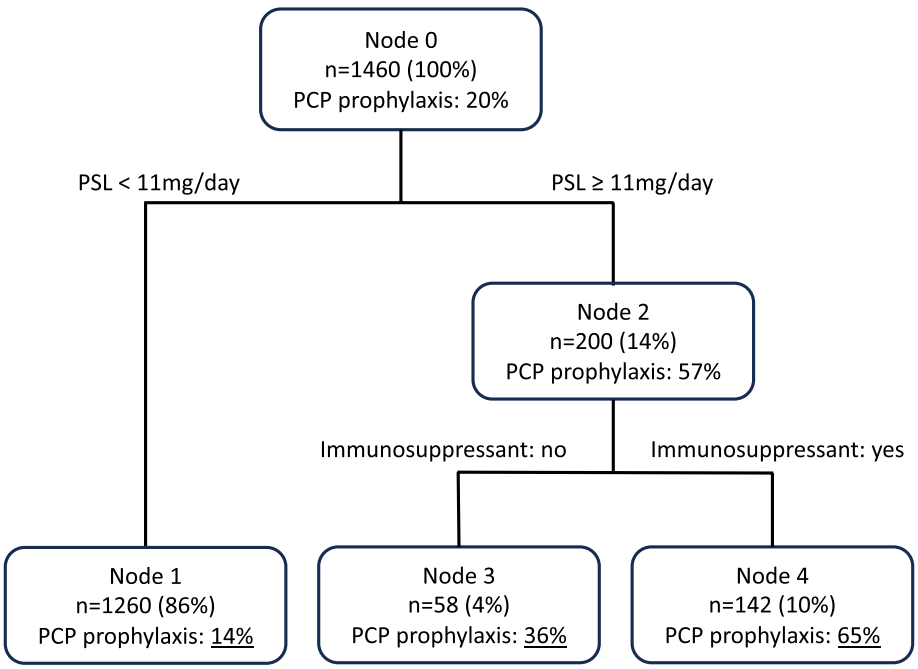

Fig. 1 Decision tree analysis of factors influencing *Pneumocystis* pneumonia prophylaxis

dataset according to PCP prescriptions, first with PSL dose and then with use of immunosuppressants to create subsets with higher and lower proportions of PCP prescription (Supplemental Table 2). Of the patients with PSL < 11 mg/day, which accounted for 86% of the enrolled patients, 14% underwent PCP prophylaxis. Of these patients, 36% of those without and 65% of those with immunosuppressants underwent PCP prophylaxis.

Discussion

In the present study, we focused on PCP prophylaxis in a clinical setting in patients with SLE. Among the enrolled patients, approximately 20% had PCP prophylaxis. We observed that the proportion of patients receiving PCP prophylaxis decreased with a decrease in GC dosage. Even after adjusting for confounders, the GC dosage remained associated with PCP prophylaxis, and decision tree analysis identified GC dosage and immunosuppressant use as determining factors influencing PCP prophylaxis.

Patients with SLE received PCP prophylaxis in a manner dependent on GC dosage. The minimum GC dosage at which PCP prophylaxis is recommended remains unclear; however, current evidence suggests a threshold of > 15 to 30 mg/day of PSL [13]. A previous report indicated that PCP prophylaxis was continued until the day patients with rheumatic diseases were prescribed ≤ 15 mg/day of PSL; half of these patients had SLE [14]. According to a study using administrative claim data on patients with SLE, 14% of patients overall were on PCP prophylaxis, while 74% of patients with ≥ 20 mg of PSL were on PCP prophylaxis [15]. Similar to a previous report, our study found that 20% of all patients received PCP prophylaxis and 68% of those on ≥ 20 mg of PSL. Combined with the fact that there was an extreme difference in PCP prevention rates between Group 5 (PSL ≥ 20 mg) and Group 4 (10 ≤ PSL < 20 mg) (68% vs. 36%) in our study, physicians' empirical threshold for starting or continuing PCP prophylaxis may be around 15 to 20 mg/day of PSL.

Concomitant use of immunosuppressants is also an important determinant of PCP prophylaxis. Given the risk of PCP associated with the concomitant use of GCs and immunosuppressants [14, 16, 17], PCP prophylaxis is recommended for patients receiving GCs, especially those receiving concomitant immunosuppressants [13]. Considering other factors related to PCP in SLE, such as lymphocytopenia, disease activity, and hydroxychloroquine use [8, 18], our decision-tree analysis highlighted the importance of GC dosage and immunosuppressant use as determinants. The inclusion of many patients in the maintenance phase of remission in this study suggests that the decision to terminate PCP prophylaxis is based more on the medication type and dosage than on disease activity or laboratory data.

This study has some limitations. First, many of the enrolled patients did not require PCP prophylaxis. However, this study had a sufficiently large sample size to include a certain number of patients with a high GC dosage. Furthermore, the present study allowed us to consider the timing of the termination of PCP prophylaxis, as it is likely that some patients had previously received PCP prophylaxis but had already terminated it. Second, the safety impact of TMP/SMX has not been evaluated; adverse events of TMP/SMX have been reported to be more common in patients with SLE [9, 19], and some patients may not be on PCP prophylaxis because of adverse events. In the present study, the inclusion of pentamidine and atovaquone in the evaluation ensured the validity of PCP prophylaxis. Third, since this is a cross-sectional study, it is not possible to assess glucocorticoids dosage over time. Even the same GC dose at a single point in time may change the degree of concern of physicians about the development of PCP, depending on the length of use and cumulative dose to date. As a result, PCP prophylaxis may continue at lower doses in patients who have been using for a longer period of time. Fourth, confounding by indication must also be considered. For example, general conditions such as activities of daily living may be a confounding factor, although not adjusted for in this study. Finally, the present study only evaluated treatment practice patterns and did not assess the actual prevention efficacy. Therefore, it was not possible to determine whether the current treatment was excessive or insufficient. However, the fact that clinicians were less likely to prevent PCP in patients with PSL < 11 mg/day or no immunosuppressants prescribed indirectly suggests that these patients are less likely to develop PCP. We believe that this empirical cutoff is conservative enough to prevent PCP and is likely to be a cutoff at which non-inferiority can be safely demonstrated in future intervention studies. Regardless, the prescribing characteristics identified in this study could assist clinicians in deciding when to discontinue PCP prophylaxis.

Conclusions

This study elucidates the patterns of PCP prophylaxis in patients with SLE, highlighting a significant association with GC dosage and the concomitant use of immunosuppressants. Despite limitations, this research contributes valuable insights into the practice patterns of PCP prophylaxis among patients with SLE.

Abbreviations

PCP	*Pneumocystis jirovecii* Pneumonia
GC	Glucocorticoid
SLE	Systemic lupus erythematosus

PSL	Prednisolone
TMP/SMX	Trimethoprim/sulfamethoxazole
LUNA	Lupus Registry of Nationwide Institutions
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC-DI	Systemic Lupus International Collaborating Clinics Damage Index
Ig	Immunoglobulin

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Authors' contributions
TO, KS, KH and TY made substantial contributions to the conception and design of the study. TO, KS, YM, RY, YS, SO, HK, KI, SS, MF, NY, TK, YM, KN, and TY made substantial contributions to the acquisition of data. TO, KS and KH analyzed and TO, KS, KH, YM, RY, YS, SO, HK, KI, SS, MF, NY, TK, YM, KN, and TY interpreted the patient data. TO and KS were the major contributor to writing of the manuscript. KH, YM, RY, YS, SO, HK, KI, SS, MF, NY, TK, YM, KN, and TY helped to revise the manuscript. All authors read and approved the final manuscript.

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Data Availability
The datasets used and analyzed in the present study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and informed consent
This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Epidemiologic Research in Japan. The study protocol was approved by the Ethics Committee of Kakogawa Central City Hospital (authorization number: 2021–04). The patients provided written informed consent to participate in the and permission to publish their data.

Consent for publication
Not applicable.

Competing interests
KS received speaker fees from Glaxo Smith Kline and a research grant from Pfizer Inc. TY received speaker fees from Glaxo Smith Kline.

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