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Adjunctive Corticosteroids decreased the risk of mortality of non-HIV Pneumocystis Pneumonia

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ABSTRACT

Objectives: A mortality rate of non-human immunodeficiency virus–infected pneumocystis pneumonia (non-HIV PCP) is 30–60%. But the effectiveness of adjunctive corticosteroids with trimethoprim–sulfamethoxazole has been unclear, and we examined whether it lowered risk of mortality in non-HIV PCP.
Methods: We did an observational study of adult non-HIV PCP patients from April 2010 through March 2016, using Japanese nationwide healthcare records of the Diagnostic Procedure Combination database (DPC). The risk was estimated by the time-dependent Cox regression analyses with inverse probability weights.
Result: 1299 eligible non-HIV PCP patients were identified. 737 patients were severe respiratory status (partial pressure of oxygen in arterial blood [PaO_2] ≤60 mm Hg) and 562 were moderate (PaO_2 >60 mm Hg) at hospital admission. Among patients with severe respiratory status, the adjunctive corticosteroids was associated with lower risk of 60-day mortality (HR 0.71; 95% confidence interval [CI], 0.55–0.91), and significantly decreased mortality rates (24.7% vs 36.6%, P = 0.006). In contrast, no significant differences were observed in the risk of 60-day mortality (HR 1.17; 95% CI, 0.73–1.86) and the mortality rate (10.9% vs 9.1%, P = 0.516) among patients with moderate respiratory status.
Conclusion: The adjunctive corticosteroids were associated with lower risk of 60-day mortality in severe non-HIV PCP patients.

Introduction

Pneumocystis pneumonia is a known opportunistic infection affecting immunocompromised patients, such as those with HIV/AIDS, cancer, transplantation, rheumatoid arthritis and other connective tissue diseases, and immunodeficiency. These patients are usually treated with immunosuppressant drugs, including corticosteroids, anticancer drugs, biological drugs such as tumor necrosis factor alpha (TNF-alpha) inhibitor or interleukin-6 (IL-6) receptor inhibitor, and other immunosuppressants. The mortality rate of human immunodeficiency virus-uninfected pneumocystis pneumonia (non-HIV PCP) patients is 30–60%, and 10–20% in HIV-infected pneumocystis pneumonia (HIV PCP) patients (Thomas and Limper, 2004). Several randomized trials or meta-analyses in HIV-PCP patients have provided credible evidence of treatment with adjunctive corticosteroids with trimethoprim–sulfamethoxazole (TMP–SMX), which has been widely used and reduced mortality of HIV PCP patients (National Institutes of Health, 1990; Ewald et al., 2015; AIDSinfo, 2018). However, it remains unclear whether adjunctive corticosteroids with TMP–SMX reduce mortality in non-HIV PCP patients. Since past observational studies of adjunctive corticosteroids for non-HIV PCP patients had relatively small sample size (Median sample size, 82 [interquartile range, [IQR], 28–113) (Injean et al., 2017) or lacked stratification of respiratory status in detail, a definitive conclusion is unclear (Pareja et al., 1998; Delclaux et al., 1999). In addition, a randomized clinical trial will likely not be conducted due to the rarity of non-HIV PCP infection (McKinnell et al., 2014). In this situation, we

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aimed to elucidate the effectiveness and appropriate dose of adjunctive corticosteroid therapy with TMP–SMX for non-HIV PCP patients comprehensively and to find the optimal respiratory strata for the application of adjunctive corticosteroids therapy with adequate sample size by using the nationwide database of the real world.

Methods

Data source

In this retrospective observational study, data were obtained from the Diagnostic Procedure Combination (DPC) database in Japan as real-world data (Hamada et al., 2012). The "real-world" in the region of medicine means the information related to health care from diverse data source; electronic health records, claims and billing, disease registries, healthcare devices or software (Sherman et al., 2016; Corrigan-Curay et al., 2018). DPC has key objectives to implement a standardized electronic claims system and to provide transparency of hospital performance by the Ministry of Health, Labour and Welfare (MHLW) of Japan from 2002. The DPC database is used to identify, track, and analyze national trends of health care utilization, access, quality, outcomes, and costs. Nowadays, >1500 hospitals are participating and inputting their medical records to the DPC database, and these hospitals covered >50% number of the hospital beds in Japan. The DPC contains diverse information about hospitalized patients: sex, age, body weight, date of admission and discharge, medications and medical practices on a daily basis, diagnosis, comorbidity, complications during hospitalization, outcome, severity of diseases like pneumonia, cardiac diseases, hepatitis or cancer, and score of activity of daily living. The diagnosis and all of the other records of DPC database were entered by medical doctors in charge and professional health information managers who received professional education and examinations for qualification to manage electric healthcare records. The study was approved by the Institutional Review Board at Tokyo Medical and Dental University (M2000-788).

Study population

All patients admitted to the hospital and diagnosed with non-HIV PCP were identified from the DPC database from April 1, 2010 to March 31, 2016 (Figure 1). During the 6-year observational period, 3527 patients were admitted to the hospital for pneumocystis pneumonia without HIV. The following inclusion criteria were applied: age ≥ 18 years; non-HIV PCP; treatment by TMP–SMX with or without adjunctive corticosteroids, but not by pentamidine, atovaquone, dapsone, or any other anti-PCP drugs. After applying the inclusion criteria, 1299 non-HIV PCP patients from 457 hospitals were included. Patients were stratified by respiratory severity (moderate: PaO_2 >60 mm Hg, severe: PaO_2 ≤60 mm Hg), and classified into two groups based on their treatment history; 101 patients with moderate respiratory status and 76 of those with severe status were treated by TMP–SMX only as TMP–SMX only group, and 458 of those with the moderate and 661 of those with the severe were treated by TMP–SMX with an adjunctive corticosteroids during hospitalization as Adjunctive Corticosteroids group.

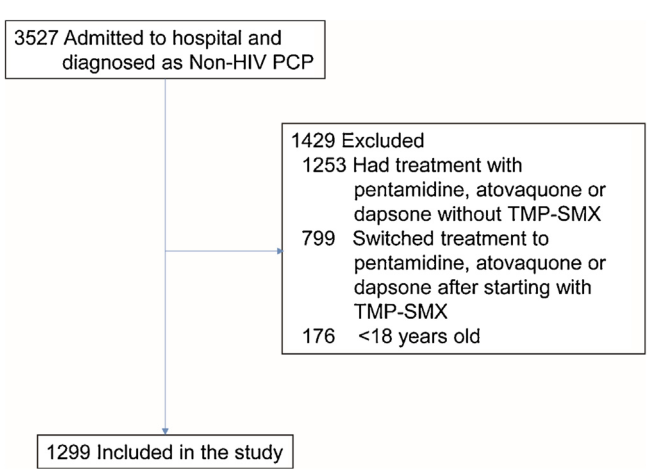

Figure 1. Flowchart of the Study and Analysis.

Definition of treatment of non-HIV PCP

Prescription information about TMP–SMX and corticosteroids was obtained on a daily basis. Unless noted otherwise, the TMP–SMX dose was described based on the trimethoprim (TMP) component from single strength 80 mg/400 mg TMP–SMX with mg per kg body weight per day as the unit (mg/kg/day). The TMP-SMX based on >15 mg/day/kg TMP component was defined as a treatment of non-HIV PCP. The adjunctive corticosteroids were defined <250 mg/day corticosteroids, except a pulse steroid therapy, administered with TMP-SMX based on ≥15 mg/day/kg of TMP component. The dose of corticosteroids was converted to the equivalent prednisolone dose. We distinguished daily administration of the adjunctive corticosteroids from the high dose pulse steroid therapy which refers to the administration of ≥250 mg prednisone equivalent a day for one or a few days (usually less than 5 days), based on standardized nomenclature of glucocorticoid dosage and glucocorticoid treatment regimens (Buttgereit et al., 2002, 2004). The pulse steroids therapy is normally used for rescue at diverse situations, for example, such as acute respiratory distress syndrome (ARDS), nephrotic syndrome, rapidly progressive glomerulonephritis, systemic vasculitis, systemic lupus erythematosus, acute renal allograft rejection, juvenile rheumatoid arthritis, juvenile dermatomyositis, pemphigus, optic neuritis, multiple sclerosis or acute disseminated encephalomyelitis etc. (Sinha and Bagga, 2008). The pulse steroid therapy is supposed to be mediated through non-genomic actions within the cell, but the adjunctive corticosteroids for PCP is normally less than 100 mg/day corticosteroids per day (Ewald et al., 2015) and the mechanism is different from pulse steroid therapy, supposed to be mediated mainly through genomic effects (Buttgereit et al., 2002). Therefore the pulse steroid therapy was considered as a different covariate from the adjunctive corticosteroids and used for the covariate adjustment in the time-dependent Cox regression analysis with inverse propensity weighting.

Study outcomes

The primary outcome was 60-day all-cause mortality. The secondary clinical outcome was the number and the duration of mechanical ventilation during hospitalization.

Statistical analysis

Since our data had several missing values, multiple imputation chained equation (MICE) (Buuren van and Groothuis-Oudshoorn, 2011) was used for multiple imputation, and subsequent sensitivity analysis was performed to inspect the type of missing values and stability of datasets. After multiple imputation, the datasets were stratified by moderate respiratory status (PaO_2 >60 mm Hg) or severe (PaO_2 ≤60 mm Hg), and hazard ratio was calculated by time-dependent Cox regression with pooling estimated values by Rubin's rule (Rubin, 1976). Baseline information was used as a time-independent covariate: sex, age, comorbidity based on the ICD-10 code and a severity of pneumonia at admission by Japan Respiratory Society community-associated pneumonia severity index (A-DROP scoring system) (Shindo et al., 2008). A-DROP is the scoring system based on CURB-65 score (Lim et al., 2003) (confusion, BUN > 20 mg/dL, respiratory rate ≥ 30 breaths/min, systolic BP <90 mm Hg or diastolic BP ≤60 mm Hg, and age ≥ 65 years), which was modified for Japanese patients clinical prediction rule for assessing the following parameters: (1) age (men ≥ 70 years; women ≥ 75 years); (2) dehydration (BUN concentration ≥ 21 mg/dL); (3) respiratory failure (saturation by pulse oximetry < 90% or PaO_2 <60 mm Hg); (4) disturbance of consciousness; and (5) low blood pressure (systolic blood pressure <90 mm Hg). The TMP–SMX dose (mg/kg/day based on TMP component), corticosteroids (converted to prednisolone dose equivalent), oxygen inhalation and mechanical ventilation were assessed as time-varying covariates on a daily basis. These time-independent and time-varying covariates were used for calculating inverse probability weights (IPW) as marginal structure model (Cole and Hernán, 2008), to reduce treatment-selection bias and time-dependent confounding. The hazard ratios were calculated by the time-dependent Cox regression with IPW adjustment and with the method of generalized estimating equations where the

Table 1
Baseline Characteristics before and after Inverse Probability Weight Adjustment.

Moderate (PaO_2 >60 mm Hg)						
	Unadjusted			IPW adjusted		
	TMP-SMX Only (n = 101)	Adjunctive Corticosteroids (n = 461)	*P* Value	TMP-SMX Only (n = 88)	Adjunctive Corticosteroids (n = 458)	*P* Value
Age,mean (SD), year	59.7 (16.3)	63.6 (13.7)	0.019	62.3 (16.9)	63.1 (13.9)	0.677
Body weight,mean (SD), kg	57.2 (13.1)	54.4 (10.2)	0.046	55.0 (12.9)	54.7 (10.4)	0.837
Sex						
Female	32 (31.7%)	206 (44.7%)	0.020	33 (37.5%)	197 (43.0%)	0.389
Male	69 (68.3%)	255 (55.3%)		55 (62.5%)	261 (57.0%)	
Pneumonia severity of A-DROP system						
Dehydration	17 (16.8%)	110 (23.9%)	0.130	21 (23.9%)	107 (23.4%)	0.940
Disturbance of consciousness	4 (4.0%)	20 (4.3%)	0.883	3 (3.4%)	20 (4.4%)	0.880
Systolic BP <90 mm Hg	7 (6.9%)	24 (5.2%)	0.591	5 (5.7%)	25 (5.5%)	0.942
Comorbidity						
After transplantation	1 (1.0%)	15 (3.3%)	0.235	1 (1.1%)	14 (3.1%)	0.351
Solid tumor	16 (15.8%)	80 (17.4%)	0.881	16 (18.2%)	79 (17.2%)	0.924
Malignancy of lymphoid tissue	17 (16.8%)	66 (14.3%)	0.693	16 (18.2%)	68 (14.8%)	0.508
Rheumatoid arthritis (RA)	8 (7.9%)	97 (21.0%)	0.005	12 (13.6%)	89 (19.4%)	0.213
Connective tissue disease except RA	2 (2.0%)	33 (7.2%)	0.051	2 (2.3%)	30 (6.6%)	0.120
Diabetes	21 (20.8%)	81 (17.6%)	0.511	17 (19.3%)	82 (17.9%)	0.880
Pulmonary obstructive disease	2 (2.0%)	10 (2.2%)	0.927	1 (1.1%)	9 (2.0%)	0.699
Interstitial pneumonitis	4 (4.0%)	52 (11.3%)	0.026	6 (6.8%)	48 (10.5%)	0.334
ARDS	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Renal failure	1 (1.0%)	11 (2.4%)	0.441	1 (1.1%)	10 (2.2%)	0.605

Severe(PaO_2 ≤60 mm Hg)						
	Unadjusted			IPW adjusted		
	TMP-SMX Only (n = 76)	Adjunctive Corticosteroids (n = 661)	*P* Value	TMP-SMX Only (n = 71)	Adjunctive Corticosteroids (n = 661)	*P* Value
Age,mean (SD), year	66.8 (13.6)	67.5 (13.0)	0.658	67.5 (13.6)	67.5 (13.0)	0.904
Body weight,mean (SD), kg	54.5 (10.5)	54.0 (10.5)	0.694	54.0 (10.4)	54.0 (10.5)	0.909
Sex						
Female	28 (36.8%)	294 (44.5%)	0.222	29 (40.8%)	290 (43.9%)	0.961
Male	48 (63.2%)	367 (55.5%)		42 (59.2%)	371 (56.1%)	
Pneumonia severity of A-DROP scoring system						
Dehydration	35 (46.1%)	288 (43.6%)	0.880	31 (43.7%)	290 (43.9%)	0.986
Disturbance of consciousness	12 (15.8%)	93 (14.1%)	0.879	11 (15.5%)	94 (14.2%)	0.963
Systolic BP <90 mm Hg	10 (13.2%)	77 (11.6%)	0.944	9 (12.7%)	78 (11.8%)	0.975
Comorbidity						
After transplantation	2 (2.6%)	16 (2.4%)	0.976	2 (2.8%)	15 (2.3%)	0.962
Solid tumor	16 (21.1%)	133 (20.1%)	0.975	15 (21.1%)	133 (20.1%)	0.975
Malignancy of lymphoid tissue	9 (11.8%)	68 (10.3%)	0.880	8 (11.3%)	69 (10.4%)	0.974
Rheumatoid arthritis (RA)	10 (13.2%)	142 (21.5%)	0.096	13 (18.3%)	139 (21.0%)	0.881
Connective tissue disease except RA	3 (3.9%)	42 (6.4%)	0.523	4 (5.6%)	41 (6.2%)	0.973
Diabetes	18 (23.7%)	123 (18.6%)	0.335	15 (21.1%)	125 (18.9%)	0.909
Pulmonary obstructive disease	8 (10.5%)	32 (4.8%)	0.045	5 (7.0%)	35 (5.3%)	0.676
Interstitial pneumonitis	13 (17.1%)	103 (15.6%)	0.913	12 (16.9%)	104 (15.7%)	0.975
ARDS	0 (0.0%)	10 (1.5%)	0.335	0 (0.0%)	9 (1.4%)	0.393
Renal failure	2 (2.6%)	19 (2.9%)	0.976	2 (2.8%)	19 (2.9%)	0.999

ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; IPW, inverse probability weight; PaO_2, arterial oxygen pressure; RA, rheumatoid arthritis; SMD, standard mean difference.

clustering effect associated with hospitals is accounted for by the robust sandwich standard error estimator (Therneau and Lumley, 2018), because the number of the non-HIV PCP patients were diverse in each hospital among 7 years of observation period (Median of 2 cases; IQR, 1–3; maximum, 26) (Fig. S1 and Table S1 in supplementary document).

The most effective dose of the adjunctive corticosteroids was estimated using the time-dependent Cox model with restricted cubic splines. A two-sided P value of <0.05 was considered to be statistically significant. Analyses were performed using the statistical environment R software, version 3.4.3 (R Foundation).

Results

Table 1 presents the baseline characteristics of patients. There was unbalanced distribution between the two groups before weighting adjustment. The moderate respiratory status of non-HIV PCP patients had an imbalance between the Adjunctive Corticosteroids group and the TMP–SMX only group; the proportion of female (31.7% vs 44.7%; p = 0.020), dehydration (16.8% vs 23.9%; p = 0.130), rheumatoid arthritis (RA) as comorbidity (7.9% vs 21.0%; p = 0.005), the other connective tissue diseases except RA (2.0% vs 7.2%; p = 0.051) and interstitial pneumonitis (4.0% vs 11.3%; p = 0.026). The severe respiratory status also had an imbalance between treatment groups: the proportion of female (36.8% vs 44.5%; p = 0.222), rheumatoid arthritis (RA) as comorbidity (13.2% vs 21.5%; p = 0.096), and pulmonary obstructive disease (10.5% vs 4.8%; p = 0.045). These and other all imbalances between the two treatment groups were adjusted by IPW as marginal structural models (Cole and Hernán 2008), and all baseline characteristics were well adjusted between the treatment groups (Table 1). The adjusted hazard ratios (HR) for 60-day all-cause mortality in the Adjunctive Corticosteroids group of the severe non-HIV PCP were 0.73 (95% CI, 0.59–0.91) without IPW adjustment and HR 0.71 (95% CI, 0.55–0.91) with IPW adjustment (Table 2). Restricted cubic spline analysis had a range from 17 to 36 mg/day of the adjunctive corticosteroids, with HR 0.29 (95% CI, 0.18–0.46) without IPW adjustment and HR 0.29 (95% CI, 0.18–0.44) with IPW adjustment, these ranges were associated with lower risk of all-cause mortality (Table 3). In addition, we also estimated the hazard ratio of the adjunctive corticosteroids based on mg per body weight kg per day (mg/kg/day) unit, and 0.40 to 0.71 mg/kg/day of the adjunctive corticosteroids associated with lower risk of all-cause mortality in the severe non-HIV PCP, and its HR was 0.39 (95% CI, 0.24–0.61) without IPW adjustment and HR 0.37 (95% CI, 0.23–0.58) with IPW adjustment. Median (IQR) dose of the adjunctive corticosteroids was 39 (25–56) mg/day in absolute quantity and 0.72 (0.48, 1.02) mg/kg/day (Table 4). In contrast, the adjusted hazard ratios (HR) for 60-day all-cause mortality in the Adjunctive Corticosteroids group in the moderate non-HIV PCP were HR 1.10 (95% CI, 0.73–1.68) without IPW adjustment and HR 1.17 (95% CI, 0.73–1.86) with IPW adjustment (Table 2). The adjunctive corticosteroids had no significant difference for 60-day all-cause mortality for the moderate non-HIV PCP. Median (IQR) dose of the adjunctive corticosteroids was 35 (21–48) mg/day, and 0.64 (0.41–0.90) mg/kg/day (Table 4).

As a secondary outcome, a proportion of the patients using the mechanical ventilation was not significantly different between the treatment groups in both of the respiratory status (Table 4). In the moderate non-HIV PCP, the patients of 5.7% of the TMP-SMX only group and 8.5% of the Adjunctive Corticosteroids group received the mechanical ventilation (p = 0.840), and no significant difference in the 60-day mortality was observed between the treatment groups. On the other hand, in the severe non-HIV PCP, the patients of 18.4% of the TMP-SMX only group and 22.4% of the Adjunctive Corticosteroids group received the mechanical ventilation (p = 0.352), and the 60-day mortality was lower in the adjunctive corticosteroids than the TMP–SMX group (56.1% vs 84.6%, p = 0.031). Among survived patients of both of the respiratory status, the duration of the mechanical ventilation was shorter in the Adjunctive Corticosteroids group than in the TMP–SMX group. Median (IQR) duration of the mechanical ventilation was 9 (5–15) days in the TMP–SMX group vs 6 (3–14) days in the Adjunctive Corticosteroids group among the moderate non-HIV PCP, and 13 (IQR was not determined, because there was only 1 patient who received mechanical ventilation in the survived patients) vs 6 (4–10) in the severe respiratory status (Table 4).

In addition, the sensitivity and complete-case analyses were performed. First, sensitivity analyses was performed by restricting follow-up times to 30 days and restricting patients who received treatment in 72 h from hospital admission. Since our predefined follow-up time was 60 days according to past several RCTs of HIV PCP (Ewald et al., 2015) and actual hospital stay length in our cohort was median of 21 days (IQR, 14–32), these difference of follow-up time or long delay of starting treatment from hospital admission could weaken the causality between the treatment and the outcome in our study. After restriction, the results of sensitivity analyses were similar to the main analysis in both of the respiratory status (Table 5). We also performed complete-case analysis and confirmed consistency of our multiple imputation and IPW adjustment. The hazard ratios estimated from the patients of complete-case who had no missing value were similar to the results in Table 2 (Table 5). The adjunctive corticosteroids were associated with lower risk of 30-day and 60-day all-cause mortality of the severe and not of the moderate non-HIV PCP.

Discussion

In our study, adjunctive corticosteroids with TMP–SMX were associated with a lower risk of all-cause mortality of non-HIV PCP patients with severe respiratory status. In addition, as Pareja described that the adjunctive corticosteroids shortened the duration of the mechanical ventilation and may accelerate recovery in cases of non-HIV PCP (Pareja et al., 1998), the Adjunctive Corticosteroids group in our study had also shorter duration of the mechanical ventilation and less mortality in 60 days than the control group. Before and after adjusting time-dependent confounding between control and treatment groups by IPW, the hazard ratios were consistent both in 30 days and in 60 days of the observation period. In addition, we analyzed the effect of the adjunctive corticosteroids from aspects of both the absolute dose per day (mg/day) and the dose per body weight per day (mg/kg/day). The results suggested that there was an appropriate range of the dose of the adjunctive corticosteroids. If there are no conditions such as an acute exacerbation of

Table 2
Event Counts and Hazard Ratios of 60-day All-cause Mortality in the Non-HIV PCP Cohort.

Respiratory Status	TMP-SMX only	Adjunctive Corticosteroids	Unadjusted HR (95% CI)	P value	IPW adjusted HR (95% CI)	P Value
Moderate, No/Total (%)[a]	8/88 (9.1%)	50/458 (10.9%)	1.10 (0.73–1.68)	0.639	1.17 (0.73–1.86)	0.516
Severe, No/Total (%)[a]	26/71 (36.6%)	163/661 (24.7%)	0.73 (0.59–0.91)	0.005	0.71 (0.55–0.91)	0.006

Abbreviations: CI, confidence interval; HR, hazard ratio; IPW, inverse probability weight; TMX-SMX, Trimethoprim-Sulfamethoxazole.
[a] Moderate respiratory status, PaO_2 >60 mm Hg; Severe, $PaO_2 \leq 60$ mm Hg.

Table 3
Hazard Ratio according to Dose of Adjunctive Corticosteroids in severe non-HIV PCP.

	Unadjusted HR (95% CI)	*P* value	IPW adjusted HR (95% CI)	*P* value
Absolute Dose per day, mg/day				
<17	0.88 (0.60–1.32)	0.544	0.90 (0.61–1.32)	0.600
17–36	0.29 (0.18–0.46)	<0.0001	0.29 (0.18–0.44)	<0.0001
36–64	0.79 (0.50–1.27)	0.331	0.84 (0.51–1.39)	0.496
>64	0.80 (0.39–1.66)	0.564	0.71 (0.33–1.58)	0.400
Dose per body weight per day, mg/kg/day				
<0.40	0.87 (0.59–1.30)	0.519	0.74 (0.53–1.03)	0.072
0.40–0.71	0.39 (0.24–0.61)	<0.0001	0.37 (0.23–0.58)	<0.0001
0.72–1.04	0.77 (0.47–1.27)	0.308	0.68 (0.42–1.09)	0.106
>1.04	0.58 (0.26–1.30)	0.184	0.46 (0.19–1.10)	0.082

Abbreviations: CI, confidence interval; HR, hazard ratio; IPW, inverse probability weight.

Table 4
Secondary and Other Clinical Outcomes in Non-HIV PCP Patients with IPW adjustment.

	Moderate (PaO_2 >60 mm Hg)			Severe(PaO_2 ≤60 mm Hg)		
	TMP-SMX Only (n = 88)	Adjunctive Corticosteroids (n = 458)	*P* value	TMP-SMX Only (n = 71)	Adjunctive Corticosteroids (n = 661)	*P* value
Mechanical Ventilation	5 (5.7%)	39 (8.5%)	0.391	12 (16.9%)	148 (22.4%)	0.352
Patients who survived, No (% in Mechanical Ventilation)	3 (60.0%)	19 (48.7%)	0.840	1 (7.7%)	65 (43.9%)	0.031
Patients who died, No (% in Mechanical Ventilation)	2 (40.0%)	20 (51.3%)		11 (84.6%)	83 (56.1%)	
Duration of Mechanical Ventilation, median (IQR), day						
Overall Patients	9 (5–15)	6 (3–14)	0.530	10 (5–18)	9 (5–15)	0.739
Patients who survived	17 (10–74)	5 (2–8)	0.459	13 (ND[a])	6 (4–10)	ND[a]
Patients who died	9 (7–11)	12 (5–16)	0.616	9 (4–18)	12 (7–16)	0.611
Length of Stay in the Hospital, median (IQR), day	12 (7–20)	19 (14–27)	<0.0001	14 (6–25)	22 (15–32)	<0.0001
Number of Days until Death, median (IQR), day	11 (9–14)	11 (10–13)	0.913	6 (4–10)	10 (6–13)	0.0004
First Day of TMP-SMX, median (IQR), day	1 (0–2)	0 (0–2)	0.227	1 (0–2)	1 (0–2)	0.323
First Day of Adjunctive Corticosteroids, median (IQR), day		1 (0–4)			2 (0–4)	
Dose of Adjunctive Corticosteroids						
Absolute Quantity per day, median (IQR), mg/day		35 (21–48)			39 (25–56)	
Quantity per body weight per day, median (IQR), mg/kg/day		0.64 (0.41–0.90)			0.72 (0.48–1.02)	

Abbreviations: IQR, interquartile range; ND, not determined; TMP-SMX, Trimethoprim-Sulfamethoxazole.
[a] Since the number of patient was 1, variance and p-value could not be calculated.

Table 5
Sensitivity Analysis and Complete-Case Analysis.

Respiratory Status	TMP-SMX only	Adjunctive Corticosteroids	HR without IPW (95% CI)	*P* value	HR with IPW (95% CI)	*P* value
Sensitivity Analysis, Restricting follow-up time to 30 days						
Moderate, No./Total (%)[a]	7/88 (8.0%)	43/458 (9.4%)	1.03 (0.67–1.60)	0.885	1.03 (0.66–1.62)	0.900
Severe, No./Total (%)[a]	24/71 (33.8%)	141/661 (21.3%)	0.70 (0.51–0.94)	0.020	0.68 (0.50–0.93)	0.015
Sensitivity Analysis, Starting Treatment in 72 h from Hospital Admission						
Moderate, No./Total (%)[a]	5/66 (7.6%)	40/393 (10.2%)	1.60 (0.84–3.06)	0.156	1.49 (0.75–2.95)	0.252
Severe, No./Total (%)[a]	22/57 (38.6%)	142/575 (24.7%)	0.61 (0.43–0.86)	0.005	0.58 (0.42–0.81)	0.001
Complete-Case Analysis						
Moderate, No./Total (%)[a]	3/72 (4.2%)	30/345 (8.7%)	1.35 (0.86–2.11)	0.190	1.48 (0.94–2.34)	0.093
Severe, No./Total (%)[a]	19/50 (38.0%)	126/492 (25.6%)	0.61 (0.44–0.86)	0.005	0.61 (0.41–0.89)	0.011

Abbreviations: CI, confidence interval; HR, hazard ratio; IPW, inverse probability weight; TMX-SMX, Trimethoprim-Sulfamethoxazole.
[a] Moderate respiratory status, PaO_2 >60 mmHg; Severe, PaO_2 ≤60 mmHg.

comorbidities or an onset of severe illness, it seems better not to use carelessly the high dose of the adjunctive corticosteroids to non-HIV PCP. The past several studies provided evidence of the dose range of the adjunctive corticosteroids in HIV PCP patients. In the severe HIV PCP, 20–80 mg/day of the adjunctive corticosteroids was recommended for adult patients, and 0.5–1 mg/kg/day of the adjunctive corticosteroids for children (AIDSinfo, 2018; Bozzette et al., 1990; Gagnon et al., 1990; Ewald et al., 2015). The recommended dose based on body weight was unknown in non-HIV PCP patients. Our analysis with restricted cubic splines suggests the favorable range of the adjunctive corticosteroids in adults with severe non-HIV PCP. From our results, 0.40 to 0.71 mg/kg of corticosteroids are equivalent to 21.6 to 38.3 mg with the average body weight of 54.0 kg in the cohort. The average body weight is close to the Asian average of 57.7 kg described by Walpole et al. based on *WHO SURF2* report and national health examination surveys, primarily *the Demographic and Health Surveys*, in which the human body mass of about 170 countries of populations was covered (Walpole et al., 2012). If applying our results to these average body weights of North American, 32 to 57.3 mg/day of the adjunctive corticosteroids with the average body weight of 80.7 kg, this range of adjunctive corticosteroids overlaps with those widely used against HIV PCP (AIDSinfo, 2018; Bozzette et al. 1990; Gagnon et al., 1990; National Institutes of Health, 1990; Pareja et al., 1998; McKinnell et al., 2014; Ewald et al., 2015). In contrast, the adjunctive corticosteroids had no significant differences in 30- and 60-day mortality in the moderate non-HIV PCP. Our results suggest the corticosteroids in the moderate non-HIV PCP were effective to basal diseases of the patients rather the non-HIV PCP. Mortality of non-HIV PCP patients is generally higher than that of HIV PCP (Thomas and Limper, 2004). In our study, the mortality rate of 36.6% was observed in the TMP–SMX only group during 60 days of hospitalization, which was still high at 24.7%, although adjunctive corticosteroids decreased the risk of all-cause mortality. In our real-world data, solid tumor, rheumatoid arthritis and other collagen diseases had a large proportion of comorbidity of patients. Mentioned in a previous study of HIV PCP, the patients with solid tumors have a greater risk of mortality than those with rheumatoid arthritis or other connective tissue diseases (Thomas and Limper, 2004). Our results are similar to these past findings, solid tumor associated with a higher risk of the mortality in severe non-HIV PCP patients (HR 1.38; 95% CI, 1.13–1.68, data not shown). However, it has been unclear what comorbidity and medications are the risk of the progression to severe respiratory status and higher mortality of non-HIV PCP than that of HIV PCP. In HIV patients with a history of highly active antiretroviral therapy (HAART), the adjunctive corticosteroids are considered to have an anti-inflammatory effect for an inflammation caused by destroying *Pneumocystis jirovecii*, or by immune reconstitution inflammatory syndrome (IRIS) (Müller et al., 2010; Achenbach et al., 2012). Such patients demonstrated exuberant and dysregulated inflammatory responses to invading microorganisms and clinical deterioration after the initiation of HAART, despite successful virus level control and immunological recovery (Müller et al., 2010; Sharma and Soneja, 2011). HIV PCP patients develop IRIS as a paradoxical inflammatory response following the initiation of anti-PCP therapy and respond well to adjunctive corticosteroids within 72 h from the start of anti-PCP therapy (Ewald et al., 2015). The development of IRIS has been observed after discontinuation of steroid therapy and the adjunctive corticosteroids are suggested to play a role for a reintroduction of steroids (Sharma and Soneja, 2011). IRIS and similar disease statuses were reported in non-HIV patients with corticosteroid withdrawal, discontinuation of biologics such as tumor necrosis factor alpha (TNF-alpha) inhibitor or interleukin-6 (IL-6) receptor inhibitor, immunosuppression in transplant recipients, recovery from neutropenia after cytotoxic chemotherapy, and engraftment of stem-cell transplantation (Cheng et al., 2000; Cadena et al., 2009; Singh et al. 2016). Our results suggest the adjunctive corticosteroids probably targets the immune reconstitution inflammatory syndrome (IRIS) in non-HIV PCP patients as well as in those of HIV.

Limitations

There were several limitations to be considered. First, since our patient inclusion criteria in this study were based on diagnosis on the database, we could not track hidden non-HIV PCP patients who had been not diagnosed. A recent validation study showed that the DPC database had both of the sensitivity and specificity of recorded procedures exceeded 90% in the records of diagnosis, compared with laboratory test and chart information as reference standards (Yamana et al., 2017). We considered the sensitivity, specificity and quality of the DPC database recorded by medical doctors and qualified professional health information managers supports the validity of diagnosis recorded in the DPC database. Second, the DPC database is the healthcare records for inpatients and not for outpatients. Therefore we are not able to acquire the medical records before the hospitalization of the non-HIV PCP patients. Third, as shown in the baseline characteristics of our study cohort, non-HIV patients generally have various comorbidities and its proportion varies. More stratification regarding comorbidities needs a larger sample size. Therefore, further investigations are needed to identify what medications or conditions of comorbidities increase or decrease the risk of progression into severe respiratory status or mortality of non-HIV PCP, and how to prevent it.

Conclusions

Our observational study suggested the adjunctive corticosteroid with TMP–SMX decreased the risk of 30- and 60-day all-cause mortality of severe non-HIV PCP patients with severe respiratory status. In contrast, the adjunctive corticosteroids did not decrease the risk of mortality of non-HIV PCP patients with moderate respiratory status. Further study is warranted to confirm these findings.

Contributors

NI designed the study. KF collected the data and supervised. NI analyzed the data. NI and KF interpreted the data. NI drafted the manuscript. NI and KF critically revised manuscript for important intellectual content.

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

Ethical statement

The study was approved by the Institutional Review Board at Tokyo Medical and Dental University (M2000-788).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.12.001.

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