A Four-Center Retrospective Study of the Efficacy and Toxicity of Low-Dose Trimethoprim-Sulfamethoxazole for the Treatment of *Pneumocystis* Pneumonia in Patients without HIV Infection

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ABSTRACT The dose of trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of *Pneumocystis* pneumonia (PCP) in patients without human immunodeficiency virus (HIV) infection has not been verified. The aim of this study was to investigate the efficacy and toxicity of a low-dose TMP-SMX regimen in such patients. A retrospective study was conducted in four hospitals. We reviewed the medical records of patients with PCP but not HIV (non-HIV-PCP) who were treated with TMP-SMX between 2003 and 2016. The patients were divided into conventional-dose (TMP, 15 to 20 mg/kg/day) and low-dose (TMP, <15 mg/kg/day) groups after patients who received high-dose (TMP, >20 mg/kg/day) treatment were excluded. Grouping was done according to a correction dose, which was based on renal function. Eighty-two patients had non-HIV-PCP. The numbers of patients who received high-, conventional-, and low-dose treatments were 5, 36, and 41, respectively. Kaplan-Meier analysis for death associated with PCP showed no statistically significant difference in survival rates between the conventional- and low-dose groups. Ninety-day cause-specific mortality rates were 25.0% and 19.5% in the conventional-dose and low-dose groups ($P = 0.76$), respectively. Adverse events that were graded as ≥3 according to the Common Terminology Criteria for Adverse Events (version 4.0) (National Cancer Institute, 2010) were 41.7% and 17.1% in the conventional-dose and low-dose groups ($P = 0.02$), respectively. Moreover, vomiting ($P = 0.03$) and a decrease in platelet count ($P = 0.03$) occurred more frequently in the conventional-dose group. Treatment of non-HIV-PCP with low-dose or conventional-dose TMP-SMX produces comparable survival rates; however, the low-dose regimen is better tolerated and associated with fewer adverse effects.

KEYWORDS low dose, *Pneumocystis* pneumonia, renal impairment, trimethoprim-sulfamethoxazole

Pneumocystis pneumonia (PCP) is an opportunistic pulmonary infection in patients with AIDS. Antiretroviral therapy for human immunodeficiency virus (HIV) infection and chemoprophylaxis for *Pneumocystis* infection have reduced the frequency of PCP in HIV infection (HIV-PCP) (1). In contrast, having PCP but not HIV infection (non-HIV-PCP) is a growing concern as the number of patients receiving transplantation, corticosteroids, immunosuppressants, biological agents, and antitumor chemotherapy is increasing.

The clinical characteristics and immunological profiles of non-HIV-PCP are different

from those of HIV-PCP. Non-HIV-infected patients do not usually show a decline in $CD4^+$ cell counts. HIV-infected patients with $CD4^+$ cell counts of less than 200 cells/μl have the highest risk of developing PCP (2, 3). Although non-HIV-infected patients typically have a smaller number of *Pneumocystis* organisms in their lungs than HIV-infected patients, non-HIV-infected patients usually have more severe bronchoalveolar lavage fluid neutrophilia and a greater inflammatory response (4, 5). The severity of non-HIV-PCP is higher with a more rapid and fulminant onset. The mortality rates associated with non-HIV-PCP and HIV-PCP are approximately 30 to 60% and 10 to 20%, respectively (3).

The treatment for PCP was recommended based on findings of randomized controlled trials conducted mostly in HIV-PCP patients. There is no well-established regimen for treating non-HIV-PCP. HIV-PCP and non-HIV-PCP are similarly treated although they are different in pathophysiology. According to current guidelines for the prevention and treatment of opportunistic infections in HIV-infected patients, the preferred treatment for PCP is oral or intravenous trimethoprim-sulfamethoxazole (TMP-SMX; TMP, 15 to 20 mg/kg/day; SMX, 75 to 100 mg/kg/day) for 21 days (6). However, clinicians often have to reduce the dose or switch to an alternative treatment due to the occurrence of adverse events (7).

A few studies have been conducted on the treatment of PCP with lower doses of TMP-SMX in order to reduce the occurrence of adverse events. Thomas et al. (8) reported that low-dose TMP-SMX (TMP, 10 mg/kg/day) and the conventional dose have comparable efficacies for HIV-PCP treatment. Moreover, the low-dose regimen is associated with fewer adverse effects. Creemers-Schild et al. (9) also reported that intermediate-dose TMP-SMX (TMP, 10 to 15 mg/kg/day) and the conventional dose have similar efficacies in the treatment of HIV-PCP and non-HIV-PCP. The authors reported that using low-dose TMP-SMX (TMP, 4 to 6 mg/kg/day), depending on the clinical course of the disease, did not compromise treatment outcome.

Patients with PCP and renal impairment have to be treated with a lower dose of TMP-SMX. To date, there are no reports on the appropriate dose of TMP-SMX for treating non-HIV-PCP with careful consideration of renal function. In the present study, we aimed to investigate the appropriate dose of TMP-SMX for treating non-HIV-PCP. We compared the efficacy and toxicity of a low-dose TMP-SMX regimen with those of the conventional-dose regimen, while making dose adjustments based on the renal function of each patient.

RESULTS

Characteristics of patients. During the study period, 82 patients with non-HIV-PCP were identified. After adjustments were made based on renal function, five patients were excluded from the study because they received a high dose of the treatment, whereas the remaining patients were divided into conventional-dose ($n = 36$) and low-dose ($n = 41$) groups. The demographic and clinical features of patients in the two groups at the initiation of treatment are shown in Table 1. Body weight and creatinine clearance (CrCL), which affect calculation of the correction dose, were higher in the low-dose group. The differences in body mass indexes and parameters of severity, such as the arterial partial pressure of oxygen/fraction of inspiratory oxygen (PaO_2/FiO_2) ratio, alveolar-arterial oxygen difference (A-a DO_2), and sequential organ failure assessment (SOFA) score, between the two treatment groups were not statistically significant. Of the 77 patients studied, 16 (20.8%) had CrCL values of $\geq$30 ml/min but <50 ml/min, 8 (10.4%) had CrCL values of $\geq$15 ml/min but <30 ml/min, 2 (2.6%) had CrCL values of <15 ml/min, and 4 (5.2%) were undergoing hemodialysis.

Collagen vascular disease (42.9%), particularly rheumatoid arthritis (24.7%), was the most frequent underlying disease, followed by hematological malignancies (22.1%), solid tumors (16.9%), and interstitial lung disease (3.9%). Several patients were undergoing long-term corticosteroid treatment with or without other agents such as immunosuppressants, biologics, and antitumor drugs. The remaining 16.9% of the patients were not receiving corticosteroid treatment; however, they were receiving treatment

TABLE 1 Demographic and clinical features of patients in the two treatment groups at the initiation of treatment

Parameter[a]	Value for the parameter[b]			
	Total patient population (n = 77)	Conventional-dose group (n = 36)	Low-dose group (n = 41)	P value
Clinical characteristics				
Age (yr)	66.1 ± 13.7	67.0 ± 14.1	65.4 ± 13.2	0.49
Gender (no. of male patients/no. of female patients)	47/30	19/17	28/13	0.16
Body wt (kg)	54.8 ± 10.5	51.2 ± 9.4	57.9 ± 10.4	0.008
Body mass index (kg/m²)	21.4 ± 3.4	20.9 ± 3.5	21.9 ± 3.3	0.4
Underlying disease (no. of patients [%])				
Collagen vascular disease	33 (42.9)	18 (50.0)	15 (36.6)	0.24
Rheumatoid arthritis	19 (24.7)	11 (30.6)	8 (19.5)	0.26
Hematological malignancy	17 (22.1)	8 (22.2)	9 (22.0)	0.98
Solid tumor	13 (16.9)	5 (13.9)	8 (19.5)	0.51
Interstitial lung disease	3 (3.9)	1 (2.8)	2 (4.9)	0.63
Others	11 (14.3)	4 (11.1)	7 (17.1)	0.46
Therapy for underlying disease (no. of patients [%])				
Corticosteroid only	35 (45.5)	16 (44.4)	19 (46.3)	0.87
Corticosteroid with other agents	29 (37.7)	13 (36.1)	16 (39.0)	0.79
Without corticosteroids	13 (16.9)	7 (19.4)	6 (14.6)	0.57
Primary prophylaxis with TMP-SMX (no. of patients [%])	1 (1.3)	1 (2.8)	0 (0)	0.28
Laboratory findings				
PaO$_2$/FiO$_2$ ratio	231.0 ± 96.2	238.6 ± 94.1	223.9 ± 97.5	0.58
A-a DO$_2$ (torr)	143.7 ± 129.8	119.0 ± 106.2	166.7 ± 144.7	0.35
White blood cell count (×10⁹/liter)	8.4 ± 4.3	7.5 ± 3.6	9.3 ± 4.7	0.08
Neutrophil count (×10⁹/liter)	7.2 ± 4.2	6.2 ± 3.1	8.1 ± 4.8	0.08
Lymphocyte count (×10⁹/liter)	0.8 ± 0.5	0.8 ± 0.6	0.8 ± 0.5	0.55
Hemoglobin (g/dl)	10.8 ± 2.2	10.5 ± 2.1	11.1 ± 2.3	0.23
Platelet count (×10⁹/liter)	191.2 ± 102.8	180.0 ± 88.8	201.0 ± 111.0	0.44
Total protein (g/dl)	5.5 ± 1.0	5.6 ± 1.0	5.4 ± 0.9	0.26
Albumin (g/dl)	2.7 ± 0.7	2.8 ± 0.7	2.7 ± 0.6	0.73
Lactate dehydrogenase (IU/liter)	431.5 ± 222.3	432.0 ± 250.6	431.1 ± 194.1	0.63
Urea nitrogen (mEq/liter)	28.3 ± 18.9	29.0 ± 21.2	27.8 ± 16.6	0.6
Creatinine (mg/dl)	1.4 ± 1.4	1.7 ± 1.9	1.2 ± 0.9	0.95
C-reactive protein (mg/dl)	8.9 ± 6.9	8.9 ± 5.8	8.9 ± 7.7	0.71
KL-6 (IU/ml)	1,171.9 ± 1,619.5	770.2 ± 526.7	1,487.5 ± 2,058.9	0.22
β-D-Glucan (pg/ml)	307.2 ± 1097.2	201.5 ± 248.1	400.0 ± 1,479.3	0.9
Creatinine clearance (ml/min)	59.3 ± 36.1	53.0 ± 38.0	64.8 ± 33.3	0.03
SOFA score	4.1 ± 2.7	4.2 ± 3.0	3.9 ± 2.3	0.91

[a]A-a DO$_2$, alveolar-arterial oxygen difference; PaO$_2$/FiO$_2$, arterial partial pressure of oxygen/fraction of inspiratory oxygen; SOFA, sequential organ failure assessment; TMP-SMX, trimethoprim-sulfamethoxazole.
[b]Values are presented as means ± standard deviations unless otherwise indicated.

with other agents or had systemic or local immune system defects according to their underlying diseases. Only one patient with a malignant lymphoma and undergoing chemotherapy had received primary prophylaxis with TMP-SMX prior to being diagnosed with PCP.

Treatments and outcomes. Analysis of the different treatments (Table 2) showed that the mean correction dose of TMP was 17.5 mg/kg in the conventional-dose group and 10.8 mg/kg in the low-dose group (P < 0.001). Except for this finding and the occurrence of adverse events, there were no differences in the details of treatment between the two groups. The mean duration from PCP onset to treatment initiation was 6.1 days, whereas the mean duration of treatment with TMP-SMX for PCP was 16.9 days. Although a 14-day or 21-day regimen is usually suggested for the treatment of non-HIV-PCP, 11 patients (14.3%) could not continue with treatment for 14 days due to the occurrence of adverse events or other reasons. Furthermore, seven patients (9.1%) required treatment for more than 21 days because recovery was prolonged. Twenty-three patients (29.9%) required admission into the intensive care unit. In addition, 25 patients (32.5%) required mechanical ventilation due to severe respiratory failure.

TABLE 2 Analysis of the different treatments

Treatment parameter[a]	Value for the parameter[c]			P value
	Total patient population (n = 77)	Conventional-dose group (n = 36)	Low-dose group (n = 41)	
Duration from PCP onset to treatment (days)	6.1 ± 5.2	6.3 ± 4.3	5.9 ± 5.9	0.26
TMP-SMX treatment				
Correction dose (mg/kg TMP)	14.0 ± 4.1	17.5 ± 1.9	10.8 ± 2.8	<0.001
Duration of TMP-SMX therapy (days)	16.9 ± 6.6	15.7 ± 6.1	18.1 ± 6.8	0.06
Occurrence of adverse events[b]	22 (28.6)	15 (41.7)	7 (17.1)	0.02
Dose reduction[d]	15 (19.5)	8 (22.2)	7 (17.1)	0.57
Withdrawal or change to second-line regimen[d]	10 (13.0)	7 (19.4)	3 (7.3)	0.22
Second-line regimen				
Pentamidine	6 (7.8)	5 (13.9)	1 (2.4)	0.06
Atovaquone	1 (1.3)	0 (0)	1 (2.4)	0.35
ICU admission	23 (29.9)	9 (25.0)	14 (34.1)	0.38
Mechanical ventilation	25 (32.5)	11 (30.6)	14 (34.1)	0.74
Adjunctive corticosteroid therapy	55 (71.4)	26 (72.2)	29 (70.7)	0.89

[a]CTCAE, Common Terminology Criteria for Adverse Events; ICU, intensive care unit; PCP, pneumocystis pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.
[b]CTCAE grade of ≥3.
[c]Unless noted otherwise, values are the number (percent) of patients. Other values are presented as means ± standard deviations.
[d]Dose reduction and withdrawal or change to second-line regimen were due to the occurrence of adverse events.

Among them, 6 patients required noninvasive ventilation, whereas 19 patients required invasive ventilation. Most of the patients with moderate-to-severe respiratory failure were administered adjunctive corticosteroids according to the recommended regimen for treating HIV-PCP.

Kaplan-Meier analysis of death associated with PCP showed that there was no statistically significant difference in survival rates between the two groups (log rank test; $P = 0.59$) (Fig. 1). Moreover, the 90-day cause-specific mortality rate was 25.0% in the conventional-dose group and 19.5% in the low-dose group ($P = 0.76$). In addition, 90-day all-cause mortality rates were 27.8% and 24.4% in the conventional-dose and low-dose groups ($P = 0.94$), respectively. The results showed that mortality rates were not significantly different between the two groups.

Toxicity. The frequency of adverse events with grades of ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE) (10) was higher in the conventional-dose group (41.7%) than in the low-dose group (17.1%) ($P = 0.02$). Dose reduction due to adverse events was required in 15 patients (19.5%), whereas treatment withdrawal or change to a second-line regimen due to adverse events was required in 10 patients (13.0%). Pentamidine was used as an alternative agent in six patients, whereas atovaquone was used in one patient (Table 2). Vomiting of all grades
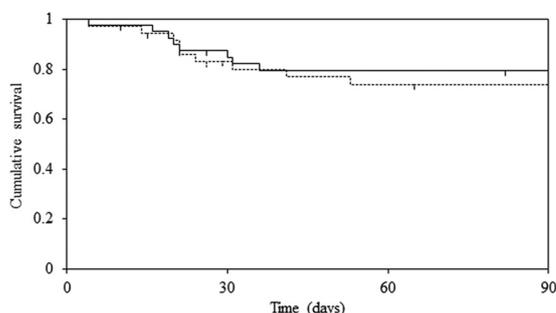
FIG 1 Kaplan-Meier survival curves for death associated with *Pneumocystis* pneumonia based on the dose of trimethoprim-sulfamethoxazole (solid line, low-dose group; dotted line, conventional-dose group). There was no statistically significant difference between the two groups. The survival curves were compared using log rank statistics. Censored subjects are indicated on the Kaplan-Meier curves as tick marks.

TABLE 3 Adverse events and their CTCAE grades

| Adverse event | Frequency by CTCAE grade (no. of patients [%])[a] | | | | | |
| | Conventional-dose group (n = 36) | | Low-dose group (n = 41) | | P value | |
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Rash	4 (11.1)	3 (8.3)	5 (12.2)	1 (2.4)	0.84	0.24
Fever	3 (8.3)	1 (2.8)	1 (2.4)	0 (0)	0.24	0.28
Anorexia	4 (11.1)	2 (5.6)	6 (14.6)	0 (0)	0.91	0.13
Vomiting	4 (11.1)	1 (2.8)	0 (0)	0 (0)	0.03	0.28
Decreased white blood cell count	3 (8.3)	0 (0)	4 (9.8)	2 (4.9)	0.83	0.18
Decreased neutrophil count	2 (5.6)	1 (2.8)	4 (9.8)	2 (4.9)	0.49	0.63
Anemia	8 (22.2)	1 (2.8)	7 (17.1)	0 (0)	0.57	0.28
Decreased platelet count	10 (27.8)	6 (16.7)	4 (9.8)	1 (2.4)	0.08	0.03
Increased aspartate aminotransferase	7 (19.4)	0 (0)	10 (24.4)	0 (0)	0.81	NA
Increased alanine aminotransferase	8 (22.2)	1 (2.8)	10 (24.4)	0 (0)	0.96	0.28
Increased creatinine	12 (33.3)	0 (0)	8 (19.5)	0 (0)	0.17	NA
Hyponatremia	12 (33.3)	4 (11.1)	11 (26.8)	1 (2.4)	0.53	0.12
Hyperkalemia	12 (33.3)	4 (11.1)	14 (34.1)	5 (12.2)	0.94	0.88

[a]CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.

(P = 0.03) and decreased platelet count of grade ≥3 (P = 0.03) were more frequent in the conventional-dose group (Table 3). Seven patients had grade ≥3 thrombocytopenia as follows: with grade 3 (platelet count, <50 ×10^9/liter), four patients in the conventional-dose group; with grade 4 (platelet count, <25 ×10^9/liter), two patients in the conventional-dose group and one patient in the low-dose group. Three patients with severe thrombocytopenia needed platelet transfusions, whereas one patient with grade 3 anemia (hemoglobin level, 5.6 g/dl) needed transfusions with packed red blood cells.

DISCUSSION

The results of the present study suggest that low-dose TMP-SMX and the conventional-dose regimen have comparable efficacies in non-HIV-PCP treatment. Moreover, the low-dose regimen was associated with a decreased occurrence of adverse events. These findings are mostly in line with those reported by Thomas et al. (8) and Creemers-Schild et al. (9). Two important differences between the present study and the previous studies were the target of the analysis, which was treatment of non-HIV-PCP only, and the determination of a low or conventional dose based on careful consideration of renal function. In the present study, 39.0% of the patients had renal impairment (CrCL, <50 ml/min) and required dose adjustment. This suggests that renal impairment is a considerable factor in determining the dose of TMP-SMX for treating PCP. Although dose adjustment methods based on renal function differ slightly in various reports (11–13), we set the correction factor according to the value of CrCL, as reported in previous studies.

Conversely, Hughes et al. (14) showed that the efficacy of high-dose TMP-SMX was superior to that of the low-dose in the treatment of non-HIV-PCP patients. The difference in the results may be due to the difference in the doses studied. Hughes et al. (14) defined high- and low-dose TMP as 20 mg/kg and 4 to 7 mg/kg, respectively. In the present study, the mean correction dose of TMP was 17.5 mg/kg in the conventional-dose group and 10.8 mg/kg in the low-dose group. Although the efficacy of the treatment was not significantly decreased in the low-dose group in the present study, it might have declined if the administered dose had been lower. These findings indicate that the appropriate dosage of TMP in a TMP-SMX regimen for non-HIV-PCP is approximately 10 mg/kg/day.

Survival rates were not significantly different between the two treatment groups. The all-cause mortality rate in the low-dose group was 24.4%, which was lower than the 30 to 60% rate reported in several studies (3). Furthermore, the severity of PCP, which is defined by PaO$_2$/FiO$_2$ and A-a DO$_2$ values and SOFA scores, was similar to that

reported in other studies (15, 16). Collagen vascular disease, particularly rheumatoid arthritis, was the most prevalent underlying disease that led to PCP in the present study. In the case of non-HIV-PCP, the mortality rate was higher in patients with neoplastic disease (34 to 50%) (17, 18) and connective tissue disease (32%) (19) but lower in those with rheumatoid arthritis (10 to 29%) (20).

The frequency of adverse events with CTCAE grades of ≥3 was significantly higher in the conventional-dose group. Particularly, the incidences of vomiting and decreased platelet count were higher in this group. Increased serum creatinine levels, hyponatremia, hyperkalemia, anemia, and neutropenia are considered concentration-dependent adverse reactions of TMP-SMX, whereas rash, fever, gastrointestinal disorders, liver function abnormalities, and thrombocytopenia are considered concentration-independent reactions (21, 22). TMP-SMX-induced thrombocytopenia appears to be an immune-mediated process resulting in platelet destruction by drug-dependent platelet antibodies (23).

The present study had some limitations. First, it was a retrospective study; therefore, it is probable that there was selection bias regarding the various treatments. Physicians decide on the dose of TMP-SMX to administer to a patient after considering body weight, CrCL, and other factors such as complications and drug interactions. Such good decisions might have caused the survival rate in the low-dose group to be comparable with that in the conventional-dose group. Second, it was uncertain if efficacy and toxicity were dependent on serum concentrations of TMP-SMX as they were not measured. We believe that since grouping was done according to the correction dose, which was calculated based on renal function, the results of the present study will help physicians to decide the appropriate doses of TMP-SMX for patients. Third, the only data on survival rate was that the difference observed between the two treatment groups was not statistically significant. Further prospective randomized controlled studies are needed to clarify the equivalence of the two regimens.

In conclusion, the survival rate following treatment of non-HIV-PCP with low-dose TMP-SMX is similar to that with the conventional-dose regimen. Moreover, the low-dose regimen is well tolerated and associated with fewer adverse effects than the conventional-dose regimen. The present study is the first to investigate the possibility of using the low-dose regimen for treating non-HIV-PCP.

MATERIALS AND METHODS

Setting and study population. A retrospective study was conducted in the following hospitals in Nagano Prefecture (Japan): Shinshu University Hospital, Nagano Municipal Hospital, Shinonoi General Hospital, and Suwa Red Cross Hospital. We reviewed the medical records of patients diagnosed with non-HIV-PCP who were treated with TMP-SMX at the participating hospitals between January 2003 and September 2016. Patients were excluded from the study if they had initially received treatments other than TMP-SMX for non-HIV-PCP.

The study was approved by the Ethics Review Board of Shinshu University (approval number 3133). Written informed consent was not obtained since patient information was anonymized. Moreover, the methods used in the study did not require obtaining informed consent under common law and ethics.

Patients were diagnosed with non-HIV-PCP if they satisfied all the following criteria: (i) an immuno-compromised status, (ii) diffuse bilateral ground-glass opacity on chest radiography or computed tomography scans, (iii) detection of *Pneumocystis jirovecii* in respiratory specimens by traditional staining (Grocott, Diff-Quik, or Giemsa staining) or PCR assay, and (iv) significantly elevated plasma (1→3)-β-D-glucan levels. β-D-Glucan was measured using a β-D-glucan test kit (Wako Pure Chemical Industries, Osaka, Japan) or Fungitec G test MK (Seikagaku Corporation, Tokyo, Japan). Although there are various reports on the cutoff for the β-D-glucan level for the diagnosis of PCP (24–29), we defined values of at least 11 pg/ml (β-D-glucan test; Wako) or 20 pg/ml (Fungitec G test MK) as indicating infection with PCP.

Data collection. Age, gender, body mass index, underlying diseases, primary prophylaxis with TMP-SMX, duration of symptoms prior to diagnosis with PCP, laboratory values, sequential organ failure assessment (SOFA) score (30) at the initiation of treatment, dose of TMP-SMX and duration of treatment, withdrawal or change to a second-line regimen, adjunctive corticosteroid therapy, mechanical ventilation, adverse events, and treatment outcome were obtained from medical records.

Adverse events occurring during treatment with TMP-SMX were extracted from the medical records and included rash, fever, anorexia, vomiting, decrease in white blood cell count, decrease in neutrophil count, anemia, decrease in platelet count, increased plasma levels of aspartate aminotransferase and alanine aminotransferase, increased serum creatinine level, hyponatremia, and hyperkalemia. Each event was graded according to the Common Terminology Criteria for Adverse Events ([CTCAE] version 4.0) (10) as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or death related (grade 5).

TABLE 4 Correction factor based on renal function

CrCL (ml/min)[a]	Correction factor
≥50	1.0
30 to <50	1.5
15 to <30	2.0
<15 or hemodialysis	3.0

[a]CrCL, creatinine clearance.

Treatment outcome was assessed as death associated with PCP or all-cause mortality within 90 days after initiation of treatment. We used the survival rate to evaluate the efficacy of the treatment.

Definition of the two treatment groups. Patients were divided into two groups: a conventional-dose group, in which patients were administered an initial dose of TMP-SMX according to current guidelines (6), and a low-dose group, in which patients were administered a dose lower than the conventional dose. Generally, if creatinine clearance (CrCL) is 15 to 30 ml/min, it is recommended to decrease the total daily dose by half (11). In addition, dose adjustments for patients with renal impairment are described in the Sanford guide (12). The Giusti-Hayton method (13), which involves calculations using CrCL and the fraction of the dose that is excreted unchanged in urine, is also used. Dosage was reduced for patients with moderate-to-severe renal impairment. If grouping had been done based on the actual dose, patients with poor renal function would have been assigned to the low-dose group. Therefore, we grouped the patients based on their renal function. Using the above-mentioned reports as references and based on expert opinions, we calculated the original correction dose from the actual dose using a correction factor based on renal function (Table 4). In order to calculate the correction dose of TMP (milligrams/kilogram), the correction factor was multiplied by the actual dose of TMP (milligrams/kilogram/day). We also used an estimated CrCL obtained from the Cockroft-Gault formula (31) as an indicator of renal function. The conventional dose was defined as the correction dose of TMP (15 to 20 mg/kg), whereas a low dose was defined as a TMP dose of <15 mg/kg. Patients who were treated with >20 mg/kg/day of TMP were excluded from the study.

Statistical analysis. Data have been expressed as means ± standard deviations for continuous variables and as percentages for categorical variables. Categorical variables were compared using a chi-square test or Fisher's exact test, whereas continuous variables were analyzed using a Mann-Whitney U test. Time-to-event analysis was performed using Kaplan-Meier estimates and a log rank test. All tests were two-tailed, and P values of <0.05 were considered statistically significant.

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