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Original Article

Low-dose trimethoprim-sulfamethoxazole treatment for pneumocystis pneumonia in non-human immunodeficiency virus-infected immunocompromised patients: A single-center retrospective observational cohort study

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KEYWORDS
Pneumocystis pneumonia;
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Abstract *Background/Purpose:* The efficacy of low-dose trimethoprim-sulfamethoxazole (TMP-SMX) may be acceptable for the treatment of pneumocystis pneumonia (PCP) in non-human immunodeficiency virus (HIV)-infected patients, with a low incidence of adverse reactions. This study is aimed to evaluate the efficacy and safety of such a regimen for the treatment of non-HIV PCP.
Methods: We retrospectively enrolled 24 consecutive patients diagnosed with non-HIV PCP who were treated with low-dose TMP-SMX (TMP, 4—10 mg/kg/day; SMX, 20—50 mg/kg/day). Data of the conventional-dose treatment were used as reference. The primary endpoints were the 30- and 180-day survival rates from the day of treatment, and secondary endpoints were the incidence of each adverse reaction and dropout rate from the initial TMP-SMX regimen.

Abbreviations: PCP, *Pneumocystis jiroveci* pneumonia; HIV, human immunodeficiency virus; TMP-SMX, trimethoprim-sulfamethoxazole; CI, confidence interval.

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Immunocompromised patients;
Treatment

The survival rate was estimated using the Kaplan—Meier method with 95% confidence interval (CI).
Results: The median age of patients was 72 years (54.2% men), and connective tissue disease was the most frequent underlying disease (66.7%) in the low-dose group. The 30- and 180-day survival rates were 95.8% (95% CI: 88.2—100.0%) and 91.0% (95% CI: 79.9%—100.0%), respectively, in the low-dose group and 69.0% (95% CI: 54.0%—88.0%) and 51.5% (95% CI: 36.1%—73.4%), respectively, in the conventional-dose group. The total adverse reaction rate was 58.3% in the low-dose group and 72.4% in the conventional-dose group. A total of 75.0% of patients in the low-dose group and 31.0% in the conventional-dose group completed treatment with the initial regimen.
Conclusion: Low-dose TMP-SMX may be a treatment option for patients with non-HIV PCP.

Introduction

Pneumocystis jirovecii pneumonia (PCP) in non-human immunodeficiency virus (HIV)-infected patients is a severe respiratory disease with a high morality.[1] The mortality rates of PCP are 30%—60% among non-HIV-infected patients compared to 10%—20% among HIV-infected patients.[2] In addition, the incidence of non-HIV PCP is increasing worldwide with the increase in the use of biologics and molecular-targeted agents for the treatment of collagen diseases, inflammatory bowel diseases, and malignancies.[1,3]

According to current guidelines and reviews, the first-line agent for the treatment of non-HIV PCP is trimethoprim-sulfamethoxazole (TMP-SMX), because it is the most effective regimen.[1,2,4] However, a significant proportion of patients need to change the drug regimen due to its adverse reactions and low tolerability; A previous study reported that 40—50% of patients could not continue treatment with the standard dose of TMP-SMX (TMP, 15—20 mg/kg/day; SMX, 75—100 mg/kg/day).[5,6] Considering that the standard dose of TMP-SMX for the treatment of non-HIV PCP is not based on the results of randomized controlled trials and that prior studies demonstrated dose-dependent adverse reactions of TMP-SMX,[6—8] it is possible that low-dose TMP-SMX may have acceptable efficacy for the treatment of non-HIV PCP, with a low incidence of adverse reactions. However, only little evidence is available regarding the low-dose TMP-SMX regimen for the treatment of non-HIV PCP.[9—11] Therefore, the aim of the present study was to summarize our single-center experience with 24 consecutive non-HIV PCP patients who received a low-dose TMP-SMX treatment regimen (TMP, 4—10 mg/kg/day; SMX, 20—50 mg/kg/day) to elucidate the safety and efficacy of low-dose TMP-SMX for the treatment of non-HIV PCP.

Methods

Study population

We retrospectively enrolled 24 consecutive patients diagnosed with non-HIV PCP who were treated with low-dose TMP-SMX (TMP, 4—10 mg/kg/day; SMX, 20—50 mg/kg/day) by the oral or intravenous route at Kameda Medical Center from January 2006 to June 2016. Data from 29 consecutive patients with non-HIV PCP who were treated with conventional-dose TMP-SMX (TMP, 10—20 mg/kg/day; SMX, 50—100 mg/kg/day) were used as reference. PCP was diagnosed on the basis of presence of all the following criteria: (1) positive conventional staining (Grocott methenamine silver or Diff-Quick stain) or deoxyribonucleic acid examination (loop-mediated isothermal amplification or polymerase chain reaction) of respiratory specimens, such as induced sputum and bronchoalveolar lavage fluid; (2) chest radiography or computed tomography (CT) findings compatible with PCP, such as bilateral ground-glass opacity; and (3) compatible clinical symptoms, including dyspnea, cough, and fever. We excluded patients with renal dysfunction, which was defined as an estimated glomerular filtration rate of <30 mL/min/1.73 m^2, or patients receiving dialysis because their pharmacokinetics were assumed to be abnormal. The study protocol complied with the Helsinki Declaration and was approved by the Research Ethics Committee of Kameda Medical Center (#16-069-160928). The requirement for written informed consent was waived because retrospective data was collected from hospital records.

Treatment strategy

During the study period, the attending physician decided whether to administer low-dose or conventional-dose TMP-SMX. Patients were administered TMP-SMX orally (two or three times daily), but patients with swallowing or absorption disturbance were administered TMP-SMX intravenously (two or three times daily). The standard duration of treatment was 2—3 weeks, as recommended by current guidelines, and treatment was continued until the general and respiratory statuses were stable.[1,4] For almost all patients, adjunctive glucocorticoid therapy was combined with the TMP-SMX treatment, for the management of severe inflammation caused by the host, as non-HIV PCP is characterized by a severe inflammatory response evoked by few organisms.[12]

We aimed to continue the initial dose of TMP-SMX for as long as possible by managing the patients' adverse reactions, which included renal dysfunction (serum creatinine level $>$ 1.8 mg/dL), hyperkalemia (serum potassium level $>$ 5.5 mEq/L), hyponatremia (serum sodium level $<$ 130 mEq/L), liver

dysfunction (alanine amino transferase level > 2.1 times the upper limit of the normal level), skin rash, and thrombopenia (platelet count < 75,000/μL). Hyperkalemia and hyponatremia were managed with administration of calcium polystyrene sulfonate and sodium chloride, respectively. Otherwise, the dose of TMP-SMX was reduced or the TMP-SMX regimen was changed to intravenous pentamidine (4 mg/kg/day) or oral atovaquone (1500 mg/day), as recommended by international guidelines.[1,4]

Endpoints and statistical analysis

The primary endpoints were the 30- and 180-day (6-month) survival rates from the day of treatment, and secondary endpoints were the incidence of each adverse reaction and dropout rate from the initial TMP-SMX regimen. Categorical variables are presented as percentages (%), and continuous variables are presented as medians (25th to 75th percentile). The survival rate was estimated using the Kaplan—Meier method with 95% confidence interval (CI). Because the aim of this study was to provide epidemiological data of patients with non-HIV PCP who were treated with low-dose TMP-SMX, we did not perform any hypothetical testing for comparisons between the low-dose and conventional-dose TMP-SMX groups; instead, we reported the summary statistics of the low-dose TMP-SMX treatment group along with data from the conventional-dose group as reference. Statistical analyses were performed using R software package (version 3.2.3, R Development Core Team; https://www.r-project.org/).

Results

The patient-selection flow chart is illustrated in Fig. 1. Among 76 consecutive patients with PCP, 72 patients with non-HIV PCP were identified after exclusion of 4 patients with HIV PCP. We excluded 9 patients with renal dysfunction, 8 patients who received initial treatment other than TMP-SMX, 1 patient who did not receive any treatment, and 1 patient treated with high-dose TMP-SMX. Finally, we enrolled 24 patients with non-HIV PCP for low-dose TMP-SMX treatment and 29 patients for conventional-dose TMP-SMX treatment.

Patient characteristics at the initiation of TMP-SMX therapy obtained retrospectively from patient records are summarized in Table 1. The median age of the low-dose group was 72 (66—79) years, and 54.2% were men. Connective tissue disease was the most-frequent underlying disease (66.7% patients) in the low-dose group, whereas hematological malignancy, solid tumors and connective tissue disease were the most frequent underlying diseases in the conventional-dose group (27.6% patients with each). The serum sodium and potassium values were within the normal range in both groups. In addition, 62.5% of patients in the low-dose group and 75.9% of patients in the conventional-dose group required oxygen administration; further, 2 patients (8.3%) in the low-dose group underwent non-invasive, positive-pressure ventilation, and 4 patients (13.3%) in the conventional-dose group underwent intubation with mechanical ventilation. TMP-SMX administration was initiated orally in 91.7% of patients in the low-dose group and intravenously in 55.2% of patients in the conventional-dose group. The median dose of TMP administration was 6.6 (5.4—7.8) mg/kg/day in the low-dose group and 14.1 (11.7—16.5) mg/kg/day in the conventional-dose group. Most patients in both groups received adjunctive glucocorticoid therapy (Table 1).

The diagnostic evidence for PCP in our study population is shown in Table 2. Approximately 80% of the patients had dyspnea, 75% had fever, and all patients showed abnormal findings on chest radiography and CT in the both groups. In

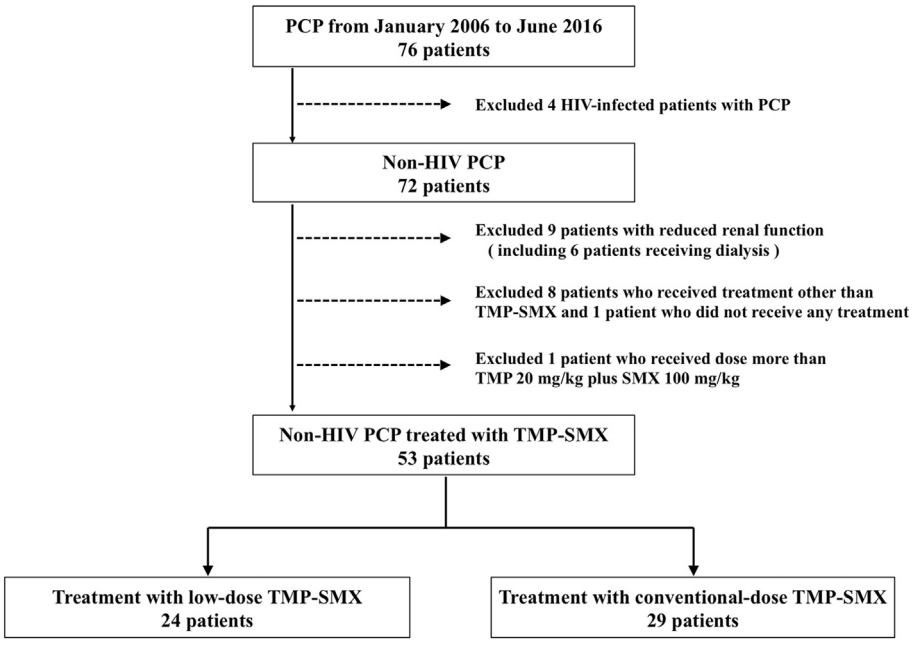


Figure 1. Patient-selection flow chart. HIV, human immunodeficiency virus; PCP, pneumocystis pneumonia; and TMP-SMX, trimethoprim-sulfamethoxazole.

Table 1 Patient characteristics at the initiation of TMP-SMX therapy.

Parameters	Missing	Low dose (n = 24)	Conventional dose (n = 29)
Age (years)	0	72 (66–79)	73 (65–81)
Male (%)	0	13 (54.2)	21 (72.4)
Weight (kg)	0	54.6 (47.1–65.0)	51.2 (43.2–61.4)
Underlying disease			
Hematological malignancy (%)	0	0 (0.0)	8 (27.6)
Solid tumors with long-term high-dose steroid treatment (%)	0	3 (12.5)	8 (27.6)
Immunosuppressive drugs for non-malignant disease (%)	0	2 (8.3)	4 (13.8)
Connective tissue disease (%)	0	16 (66.7)	8 (27.6)
Systemic vasculitis or thrombotic microangiopathy (%)	0	2 (8.3)	0 (0.0)
Idiopathic interstitial pneumonia (%)	0	1 (4.2)	1 (3.4)
Laboratory findings			
Albumin (g/dL)	0	3.0 (2.7–3.3)	2.8 (2.2–3.0)
Lactate dehydrogenase (IU/L)	0	324 (276–412)	363 (259–462)
Serum sodium (mEq/L)	0	139 (137–141)	137 (133–140)
Serum potassium (mEq/L)	0	4.3 (3.9–4.5)	4.1 (3.8–4.5)
Creatinine (mg/dL)	0	0.73 (0.61–0.91)	0.79 (0.60–0.90)
eGFR (mL/min/1.73 m^2)	0	62.8 (43.5–77.4)	65.7 (53.0–73.0)
Platelet (μg/dL)	0	19.3 (16.0–24.3)	17.9 (13.6–22.2)
Bilirubin (mg/dL)	1	0.50 (0.40–0.63)	0.65 (0.50–0.80)
Disturbed consciousness (%)	0	1 (4.2)	1 (3.4)
Hypotension (systolic pressure < 90 mmHg) (%)	0	2 (8.3)	3 (10.3)
Respiratory status			
Without oxygen (%)	0	9 (37.5)	7 (24.1)
Oxygen through nose (1–4 L/min) (%)	0	12 (50.0)	12 (41.4)
Oxygen with conventional mask (5–7 L/min) (%)	0	1 (4.2)	2 (6.9)
Oxygen with reservoir mask (8–15 L/min) (%)	0	0 (0.0)	4 (13.8)
Non-invasive positive-pressure ventilation (%)	0	2 (8.3)	0 (0.0)
Intubation with mechanical ventilation (%)	0	0 (0.0)	4 (13.8)
Route of TMP-SMX administration			
Oral (%)	0	20 (83.3)	12 (41.4)
Oral to intravenous (%)	0	2 (8.3)	1 (3.4)
Intravenous (%)	0	1 (4.2)	9 (31.0)
Intravenous to oral (%)	0	1 (4.2)	7 (24.1)
Dose of TMP administration (mg/kg/day)	0	6.6 (5.4–7.8)	14.1 (11.7–16.5)
Dose of SMX administration (mg/kg/day)	0	33.0 (27.1–39.2)	70.6 (58.6–82.6)
Duration of TMP-SMX administration (days)	0	17 (14–20)	12 (9–17)
Adjunctive glucocorticoid therapy			
None (%)	0	1 (4.2)	3 (10.3)
Prednisolone, 10 mg–75 mg/day (%)	0	11 (45.8)	10 (34.5)
Prednisolone, 80 mg–156 mg/day (%)	0	4 (16.7)	9 (31.0)
Methylprednisolone, 500 mg–1000 mg/day (%)	0	8 (33.3)	7 (24.1)

Categorical variables are shown as number (%) and continuous variables are shown as median (25th–75th percentile).
eGFR, estimated glomerular filtration rate; and TMP-SMX, trimethoprim-sulfamethoxazole.

the low-dose group and the conventional-dose group, 5 patients (20.8%) and 15 patients (51.7%) showed a positive reaction to conventional staining, whereas all patients (100.0%) and 24 patients (82.8%) showed a positive reaction to deoxyribonucleic acid examination, respectively.

Data on initial presentations, underlying diseases, use of immunosuppressants, respiratory status, presence of ground-glass opacity on chest CT, test (polymerase chain reaction, loop-mediated isothermal amplification, or Diff-quick stain) used to confirm the diagnosis, and the dose of adjuvant steroid among the 24 cases in the low-dose group are summarized in Table 3.

Data on the primary and secondary endpoints are presented in Table 4 and Fig. 2. The 30-day survival rates were 95.8% (95% CI: 88.2%–100.0%) and 69.0% (95% CI: 54.0%–88.0%) and the 180-day survival rates were 91.0% (95% CI: 79.9%–100.0%) and 51.5% (95% CI: 36.1%–73.4%) in the low-dose group and conventional-dose groups, respectively. The primary cause of death was progressive respiratory failure in all 10 patients (1 patient in the low-dose group and 9 patients in the conventional-dose group) who died within 30 days from the day of treatment. Interstitial pulmonary edema requiring administration of diuretics was observed in 3 patients (12.5%) in the low-dose group and 9 patients

Table 2 Diagnostic evidence for PCP in study patients.

Parameters	Missing	Low dose (n = 24)	Conventional dose (n = 29)
Compatible clinical symptoms			
Total (%)	0	24 (100.0)	29 (100.0)
Cough (%)	0	6 (25.0)	9 (31.0)
Dyspnea (%)	0	19 (79.2)	24 (82.8)
Fever (%)	0	18 (75.0)	22 (75.9)
Imaging modalities			
Chest radiography (%)	0	24 (100.0)	29 (100.0)
Abnormal findings (%)	0	24 (100.0)	29 (100.0)
Chest CT (%)	0	24 (100.0)	29 (100.0)
Ground-glass opacity (%)	0	24 (100.0)	29 (100.0)
Diagnostic test for PCP			
Conventional staining only (%)	0	0 (0.0)	4 (13.8)
Positive (%)	0	0 (0.0)	4 (13.8)
Deoxyribonucleic acid examination (PCR or LAMP) only (%)	0	11 (45.8)	3 (10.3)
Positive (%)	0	11 (45.8)	3 (10.3)
Both (%)		13 (54.2)	22 (75.9)
Conventional staining positive (%)	0	0 (0.0)	1 (3.4)
PCR or LAMP positive (%)	0	8 (33.3)	11 (37.9)
Conventional staining and PCR or LAMP positive (%)	0	5 (20.8)	10 (34.5)

Categorical variables are shown as number (%), and continuous variables are shown as median (25th–75th percentile).
CT, computed tomography; LAMP, loop-mediated isothermal amplification; PCP, pneumocystis pneumonia; and PCR, polymerase chain reaction.

(31.0%) in the conventional-dose group, of which 5 patients died within 30 days. The total adverse-reaction rate was 58.3% in the low-dose group and 72.4% in the conventional-dose group. The rate of hyperkalemia was 12.5% in low-dose group and 24.1% in conventional-dose group, and hyponatremia occurred in 16.7% of the low-dose group and 34.5% of the conventional-dose group. A total of 75.0% of patients in the low-dose group and 31.0% in the conventional-dose group completed treatment with the initial regimen. A representative case of non-HIV PCP that was successfully treated with the low-dose TMP-SMX regimen is presented in Fig. 3.

Discussion

In the present study, we retrospectively summarized our experience with 24 cases of non-HIV PCP that were treated with low-dose TMP-SMX; while discussing our findings, we focus on the safety and efficacy of this regimen and use data from the conventional-dose treatment as reference. In our study, the low-dose group showed relatively high 30- and 180-day survival rates of 95.8% and 91.0%, respectively, with a high completion rate with the initial regimen (75.0%). Since our study is the first and the largest case series to evaluate low-dose TMP-SMX administration, with 4–10 mg/kg/day TMP and 20–50 mg/kg/day SMX, in patients with non-HIV PCP, we believe our results provide physicians with new insights into an effective treatment strategy for non-HIV PCP.

Rationale of low-dose TMP-SMX

Because of the difficulties in culturing *P. jirovecii* in vitro, the minimal inhibitory concentrations (MIC) and clinical breakpoints of any drug for the treatment of PCP could not be obtained, even for drugs of the first-line treatment regimen, such as TMP-SMX.[2] Thus, the appropriate dose of TMP-SMX for the treatment for PCP needs to be assessed by clinical studies. Based on small, non-comparable, observational studies from 1970s to 1980s, the standard dose of TMP-SMX for PCP treatment was established as 15–20 mg/kg/day TMP and 75–100 mg/kg/day SMX.[13–15] However, the low tolerability of this dose due to its adverse events is one of the main problems of this standard regimen. On the other hand, many previous studies and systematic reviews on PCP prophylaxis in both HIV and non-HIV patients reported that even 1 single-strength tablet of TMP-SMX administered once daily (TMP, 80 mg and SMX, 400 mg; equivalent to 1.1 mg/kg/day TMP and 5.7 mg/kg/day SMX for a 70-kg body) was highly effective for PCP prophylaxis.[16] The adequate dose of prophylaxis medication is usually the same as the treatment dose needed to achieve sufficient serum and tissue concentrations exceeding the MIC in many bacterial and fungal infections.[17–19] Therefore, we hypothesized that low-dose TMP-SMX, such as that included in the prophylaxis regimen of PCP, is sufficient for the treatment of non-HIV PCP. A previous retrospective study that assessed 73 patients with HIV PCP demonstrated that the in-hospital mortality was 6.8% with a TMP-SMX treatment regimen of 10 mg/kg/day TMP and 50 mg/kg/day SMX.[9] In addition, an observational cohort study of 24 patients, including 19 non-HIV and 5 HIV patients with PCP, revealed the efficacy of the step-down TMP-SMX regimen from intermediate (TMP, 10–15 mg/kg/day; SMX, 50–75 mg/kg/day) to low-dose TMP-SMX (TMP, 4–6 mg/kg/day; SMX, 20–30 mg/kg/day), with a 30-day mortality rate of 4%.[10] On the basis of these findings, we evaluated the safety and efficacy of the low-dose TMP-SMX regimen (TMP, 4–10 mg/kg/day; SMX, 20–50 mg/kg/day) for the treatment of non-HIV PCP in this study.

Table 3 Detailed data of 24 patients with PCP treated with low-dose TMP-SMX.

Patient	Age	Sex	Initial presentation	Underlying disease (duration)	Immunosuppressant taken at the diagnosis of PCP					Respiratory status	Bilateral GGO in chest computed tomography	Diagnostic test for respiratory specimen	Initial adjunctive steroid (mg/day)
					PSL (mg/day)	MTX (mg/week)	Others DMARDs	Biological drugs	Anticancer chemotherapy				
1	78	F	Cough and fever for 3 days	RA (9 years)	9	8	BUC	IFX	—	Without oxygen	Yes	PCR (+)	mPSL 750
2	72	F	Cough and fever for 3 days	RA (27 years)	5	8	—	—	—	Conventional mask, 5 L/min	Yes	Diff-Quick stain (+) PCR (+)	PSL 40
3	63	F	Dyspnea for 3 days	RA (7 years)	10	—	—	—	—	Without oxygen	Yes	LAMP (+)	PSL 25
4	69	M	Fever for 3 days	ANCA-related vasculitis (4 months)	45	—	CPA	—	—	Without oxygen	Yes	Diff-Quick stain (+) LAMP (+)	PSL 45
5	74	M	Dyspnea for 7 days	RA (22 years)	15	—	CyA	—	—	Nasal, 3 L/min	Yes	LAMP (+)	mPSL 500
6	73	F	Dyspnea for 3 days	Polymyalgia rheumatica (1 year)	16	—	—	—	—	Nasal, 1 L/min	Yes	PCR (+)	PSL 80
7	71	F	Cough and dyspnea for 3 days	RA (33 years)	5	6	BUC	ETN	—	Nasal, 2 L/min	Yes	PCR (+)	mPSL 125
8	68	F	Dyspnea and fever for 5 days	RA (16 years)	5	8	—	CZP	—	Nasal, 1 L/min	Yes	PCR (+)	PSL 60
9	83	M	Dyspnea for 7 days	RA (30 years)	4.5	6	—	—	—	Without oxygen	Yes	PCR (+)	PSL 80
10	63	F	Fever for 3 days	Erythroderma (8 months)	30	—	CyA	—	—	Nasal, 3 L/min	Yes	PCR (+)	PSL 45
11	77	M	Dyspnea for 2 days	Sarcoidosis (2 years)	4	—	—	—	—	NPPV	Yes	PCR (+)	mPSL 1000
12	69	M	Fever for 7 days	Prostate cancer (1 year)	10	—	—	—	Docetaxel	Nasal, 2 L/min	Yes	PCR (+)	mPSL 1000
13	87	M	Dyspnea for 3 days	Temporal arteritis (6 years)	15	—	—	—	—	Nasal, 1 L/min	Yes	Diff-Quick stain (+) PCR (+)	PSL 30
14	81	M	Dyspnea and fever for 4 days	Colorectal cancer (1 year)	—	—	—	—	5-Fluorouracil Leucovorin Irinotecan Bevacizumab Dexamethasone	Nasal, 3 L/min	Yes	Diff-Quick stain (+) LAMP (+)	mPSL 1000
15	67	M	Dyspnea, cough, and	Dermatomyositis (10 years)	10	—	—	—	—	Nasal, 2 L/min	Yes	LAMP (+)	PSL 30

(*continued on next page*)

Table 3 (*continued*)

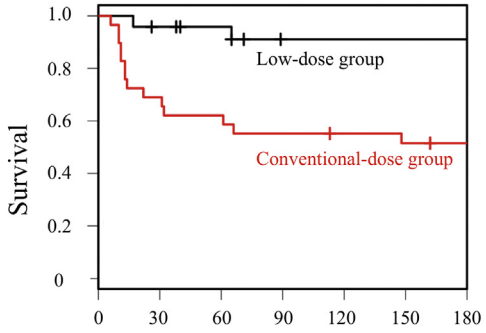
Patient	Age	Sex	Initial presentation	Underlying disease (duration)	Immunosuppressant taken at the diagnosis of PCP					Respiratory status	Bilateral GGO in chest computed tomography	Diagnostic test for respiratory specimen	Initial adjunctive steroid (mg/day)
					PSL (mg/day)	MTX (mg/week)	Others DMARDs	Biological drugs	Anticancer chemotherapy				
			fever for 7 days										
16	67	M	Fever and dyspnea for 5 days	RA (19 years)	5	6	—	—	—	Nasal, 4 L/min	Yes	PCR (+)	PSL 80
17	74	M	Dyspnea and fever for 4 days	RA (52 years)	—	10	—	—	—	Without oxygen	Yes	PCR (+)	mPSL 1000
18	48	M	Dyspnea for 7 days	Drug-induced hypersensitivity syndrome (3 months)	30	—	—	—	—	Without oxygen	Yes	Diff-Quick stain (+) LAMP (+)	—
19	64	F	Cough and fever for 9 days	RA (10 years)	1	8	—	ABT	—	Without oxygen	Yes	PCR (+)	PSL 40
20	83	F	Dyspnea and fever for 7 days	RA (40 years)	6	8	—	ETN	—	Nasal, 4 L/min	Yes	PCR (+)	PSL 50
21	86	M	Dyspnea for 20 days	RA (3 years)	10	8	—	—	—	Nasal, 3 L/min	Yes	PCR (+)	PSL 40
22	63	F	Fever and dyspnea for 5 days	ANCA related vasculitis (2 years)	6	—	AZA	—	—	Without oxygen	Yes	PCR (+)	PSL 60
23	64	M	Fever for 5 days	ACTH-producing lung cancer (1 month)	—	—	—	—	Cisplatin, Etoposide, Dexamethasone	NPPV	Yes	PCR (+)	mPSL 1000
24	87	F	Cough and fever for 6 days	Interstitial pneumonia (1 month)	20	—	—	—	—	Without oxygen	Yes	PCR (+)	mPSL 1000

ABT, abatacept; ACTH adrenocorticotropic hormone; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; BUC, bucillamine; CPA, cyclophosphamide; CyA, cyclosporin A; CZP; certolizumab; DMARDs, disease modified anti-rheumatic-drugs; ETN, etanercept; F, female; GGO, ground-glass opacity; IFX: infliximab; LAMP, loop-mediated isothermal amplification; M, male; MTX, methotrexate; NPPV, non-invasive positive-pressure ventilation; PCP, pneumocystis pneumonia; PCR, polymerase chain reaction; PSL, prednisolone; RA, rheumatoid arthritis; TMP-SMX, trimethoprim-sulfamethoxazole; and mPSL, methylprednisolone.

Table 4 Outcome data.

Parameters	Missing	Low dose (n = 24)	Conventional dose (n = 29)
Primary endpoints			
30-day survival rate (95% CI)	0	0.958 (0.882–1.000)	0.690 (0.540–0.880)
180-day survival rate (95% CI)	0	0.910 (0.799–1.000)	0.515 (0.361–0.734)
Secondary endpoints			
Adverse reactions			
Total (%)	0	14 (58.3)	21 (72.4)
Renal injury (%)	0	3 (12.5)	2 (6.9)
Hyperkalemia (%)	0	3 (12.5)	7 (24.1)
Hyponatremia (%)	0	4 (16.7)	10 (34.5)
Liver dysfunction (%)	0	6 (25.0)	6 (20.7)
Skin rash (%)	0	3 (12.5)	3 (10.3)
Thrombopenia (%)	0	2 (8.3)	3 (10.3)
Dropout rate from initial regimen			
Completion with initial regimen (%)	0	18 (75.0)	9 (31.0)
Dose reduction of TMP-SMX (%)	0	2 (8.3)	4 (13.8)
Treatment change to pentamidine (%)	0	2 (8.3)	5 (17.2)
Treatment change to atovaquone (%)	0	2 (8.3)	3 (10.3)
Termination of treatment due to adverse reaction (%)	0	0 (0.0)	4 (13.8)
Termination of treatment due to death (%)	0	0 (0.0)	4 (13.8)

Categorical variables are shown as number (%).
CI, confidence interval; and TMP-SMX, trimethoprim-sulfamethoxazole.



Number at risk

Low-dose group	24	22	20	16	16	16	16
Conventional-dose group	29	20	18	16	15	14	13

Figure 2. Kaplan–Meier survival estimate. TMP-SMX, trimethoprim-sulfamethoxazole.

Prognostic impact of low-dose TMP-SMX administration

The 30- and 180-day (6-month) survival rates of patients administered the low-dose TMP-SMX regimen were 95.8% and 91.0%, respectively, which are excellent results because the reported in-hospital mortality rates of non-HIV PCP are 30%–60%.[2,20,21] Considering that the 30-day mortality rate of the conventional-dose group was 31.0% in our study, which is similar to the previously reported mortality rate in patients with non-HIV PCP, the relatively lower mortality rate due to the low-dose TMP-SMX regimen for non-HIV PCP in our study might be worth considering.[2,20,21] We speculate that the possible mechanisms underlying this favorable outcome include (1) surpassing the MIC for *P. jiroveci* by low-dose administration based on the theory mentioned in the previous paragraph; (2) avoidance of volume overload; (3) adjunctive glucocorticoid therapy; and (4) low incidence of adverse events, as discussed in the following paragraph.

Intravenous administration of TMP-SMX requires that the drugs be dissolved in 5% glucose water. Generally, 80 mg TMP + 400 mg SMX requires 125 mL of 5% glucose water. Accordingly, intravenous administration of 15–20 mg/kg/day TMP + 5–100 mg/kg/day SMX for a body weight of 70 kg would require 2000 mL of 5% glucose water. We speculate that the fluid overload of 5% glucose water associated with conventional-dose TMP-SMX intravenous administration might lead to interstitial pulmonary edema due to the increased vascular permeability associated with inflammation, resulting in deterioration of the respiratory status and high mortality rate. In our study, among the 9 patients who died within 30 days in the conventional-dose group, 5 patients had concomitant interstitial pulmonary edema requiring administration of diuretics. Since TMP-SMX has excellent bioavailability, with nearly 100% tissue-penetration rate after oral administration,[22] the oral route should be chosen for TMP-SMX administration when possible. In addition to the low-dose TMP-SMX regimen, we used adjunctive glucocorticoid therapy for the treatment of non-HIV PCP on the basis of the fact that non-HIV PCP is characterized by a severe inflammatory response evoked by few organisms, although its efficacy for non-HIV PCP treatment is controversial, with limited data.[12,23–26]

Safety and tolerability of TMP-SMX

Administration of TMP-SMX is often complicated by adverse events, including hepatotoxicity, nephrotoxicity, bone marrow depression, and skin rash, that are sometimes an

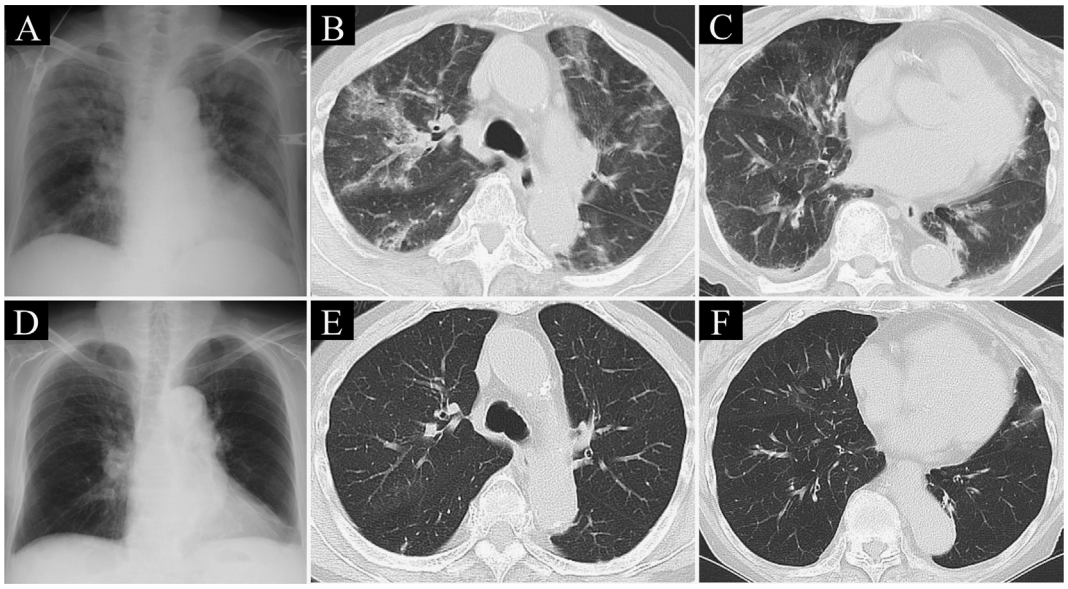


Figure 3. Representative case of non-HIV PCP that was successfully treated with low-dose TMP-SMX. An 83-year-old woman with rheumatoid arthritis who was receiving 6 mg/day prednisolone, 8 mg/week methotrexate, and etanercept was transported to our hospital for complaints of dyspnea and fever. She showed respiratory failure and received 4 L/min of oxygen therapy nasally. Chest radiography demonstrated bilateral infiltration dominantly in the upper lung fields (A), and chest computed tomography showed mosaic-like ground-glass opacity with interlobular septa thickening in bilateral lung fields (B and C). Polymerase chain reaction of Pneumocystis was positive in her respiratory sample, and she was diagnosed with non-HIV PCP. Daily oral administration of 6 mg/kg TMP + 30 mg/kg SMX (oral administration of two tablets of TMP (80 mg)-SMX (400 mg), twice daily) was initiated and continued for 17 days without any adverse events. The patient's respiratory status improved gradually, and chest radiography at 28 days after the day of treatment (D) and computed tomography at 7 days after the day of treatment (E and F) showed improvement in her condition after administration of the low-dose TMP-SMX. She was successfully discharged alive on the 18th day of hospitalization. HIV, human immunodeficiency virus; PCP, pneumocystis pneumonia; and TMP-SMX, trimethoprim-sulfamethoxazole.

obstacle to treatment completion.[1] In addition, most of these adverse events are difficult to treat with supportive medications; furthermore, change to another form of therapy or reduction of the dose of TMP-SMX is necessary to recover from these adverse events. Previous studies reported that the use of TMP-SMX for HIV-infected patients with PCP showed dose dependency for adverse reactions,[6–8] and 40%–50% of patients could not continue the standard daily dose of TMP-SMX.[5,6] Consistent with these findings, the rate of total adverse reactions was 58.3% in the low-dose group and 72.4% in the conventional-dose group in the present study. In particular, the low-dose group showed lower rates (16.7%) of hyponatremia than the conventional-dose group (34.5%). Moreover, our study showed a high completion rate with the initial regimen in the low-dose group (75.0%), while the conventional-dose group showed a low completion rate (31.0%). We speculate that the safety and high tolerability of low-dose TMP-SMX contributed to the favorable outcomes reported in this study.

Clinical implications

Our findings have important implications for clinical practice. The incidence and prevalence of non-HIV PCP are increasing worldwide with a high in-hospital morality rate of 30%–60%, and this critical issue needs to be resolved.[1] Therefore, the high efficacy and low complication rates of the low-dose TMP-SMX regimen discussed herein for the treatment of non-HIV PCP is worth validating in a prospective fashion. In the future, comparable reporting including the 30- and 180-day mortality rates, avoidance of volume overload with oral administration, presence or absence of concomitant adjunctive glucocorticoid therapy, and incidence of major adverse events should be performed to further discuss the external validity and applicability of low-dose TMP-SMX therapy for non-HIV PCP.

Study limitations

First, this was a single-center, retrospective, observational study. Second, although the number of patients enrolled in this study was the highest thus far, it is still small. Third, the characteristics of the patients differed between the low-dose group and conventional-dose group, and we avoided direct comparisons between the two regimens because of their low event rate. Compared with the conventional-dose group as a reference, none of the patients in the low-dose group had hematological malignancy (0% vs. 27.6%), received a reservoir mask (8–15 L/min) (0% vs. 13.8%), or required mechanical ventilation (0% vs. 13.8%); in addition, the low-dose group had fewer patients with solid tumors after long-term high-dose steroid treatment than the conventional-dose group (12.5% vs. 27.6%) and only one patient who received intravenous TMP-SMX (4.2% vs. 31.0%), but had more patients who did not require

oxygen therapy (37.5% vs. 24.1%). These characteristics could result in a positive effect on survival rate in the low-dose group.[27] Owing to these limitations, our findings must be interpreted with caution.

Conclusions

In the present study, the low-dose group showed that 30- and 180-day survival rates were 95.8% and 91.0%, respectively, with a high completion rate of the initial regimen (75.0%). We believe that low-dose TMP-SMX administration may be one of the treatment options for patients with non-HIV PCP. Further studies with a large cohort and randomized controlled trials are needed to confirm our results.

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Conflict of interest

All the authors declare no conflicts of interest in relation to the present study.

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