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Original Article

Effectiveness and safety of lower dose sulfamethoxazole/trimethoprim therapy for *Pneumocystis jirovecii* pneumonia in patients with systemic rheumatic diseases: A retrospective multicenter study☆

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ABSTRACT

Objectives: To evaluate the effectiveness and safety of lower-dose sulfamethoxazole/trimethoprim therapy (SMX/TMP) for *Pneumocystis jirovecii* pneumonia (PCP) in patients with systemic rheumatic diseases.

Methods: In this multicenter retrospective study, we compared effectiveness and safety of SMX/TMP for the treatment of PCP among patients divided into three groups according to the initial dosage of SMX/TMP: the low, ≤10 mg/kg/day; the intermediate, 10–15 mg/kg/day; and the high and conventional, 15–20 mg/kg/day for TMP dose.

Results: Eighty-one patients, including 22, 30, and 29 patients in the low-, the intermediate- and the high-dose group could be analyzed and the 30-day survival rate were 100%, 93.3%, and 96.7%, respectively (P = 0.28). There were significant dose-dependent increasing trends of severe adverse drug reactions (ADRs) for SMX/TMP that were graded as ≥3 according to the Common Terminology Criteria for Adverse Events. When stratified by presence of severe hypoxemia defined by alveolar-arterial O2 gradient ≥45 mmHg, the 30-day survival and treatment modification rate were similar among the three groups, but frequency of severe ADRs were significantly decreased in the low-dose group. The low-dose group was independently and negatively associated with treatment modification within 14 days and severe ADRs.

Conclusions: Lower dose SMX/TMP therapy with ≤10 mg/kg/day for TMP was as effective as higher dose therapy for the treatment of PCP and associated with lower rates of treatment modification and severe ADRs in patients with systemic rheumatic diseases.

1. Introduction

Sulfamethoxazole/trimethoprim (SMX/TMP) has been considered as the first-line therapy for the treatment of *Pneumocystis jirovecii* pneumonia (PCP), which is not an uncommon opportunistic infection seen in systemic rheumatic disease (SRD) patients

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receiving glucocorticoids and immunosuppressants in Japan [1–3]. For the treatment of active PCP, the recommended dosage is 75–100 mg/kg of SMX and 15–20 mg/kg of TMP per day given for 14–21 days according to the drug package insert in U.S. Food and Drug Administration and the guidelines from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America [4,5]. In Japan, 3600 to 4800 mg of SMX and 720–960 mg of TMP per day are also the recommended dosage for adult patients with active PCP [5,6].

The high burden of adverse drug reaction of generally recommended high-dose SMX/TMP and the limited evidence regarding optimal dose of SMX/TMP from clinical studies constrains its use. In randomized trials comparing different therapeutic options for the treatment of human immunodeficiency virus-associated PCP, patients receiving SMX/TMP at the generally recommended dosage as a standard treatment arm had higher rates of adverse events such as rash, bone marrow suppression, fever, and renal, gastrointestinal, liver dysfunction, as well as electrolyte disorders, which required switching to an alternative therapy [7–12].

These findings along with the clinical experience regarding relatively higher rates of adverse drug reactions of generally recommended SMX/TMP regimen as well as successful outcome in patients treated with lower-dose SMX/TMP, lower dose SMX/TMP therapy (2400 mg/480 mg, equivalent to six tablets of SMX/TMP) has been used in majority of cases in one of our institutions since 2006.

A small open label trial for the treatment of PCP in immunocompromised children with malignancy demonstrated numerically more patients recovered on the high-dose regimen rather than those receiving the low-dose regimen [13]. On the other hand, four retrospective studies and one small randomized trial demonstrated that treatment of PCP with two thirds of conventional dose of SMX/TMP yielded comparable effectiveness as the traditional high-dose regimen and associated with lower rates of treatment-limiting adverse events than traditional high-dose regimen [14–18].

In this multicenter retrospective study, we reviewed consecutive patients with SRD receiving immunosuppressive therapy who developed PCP and were treated with SMX/TMP as an initial *anti*-pneumocystis agent and evaluated effectiveness and safety of lower dose SMX/TMP therapy by comparing these patients originally divided into three groups according to the initial dosage of SMX/TMP.

2. Patients and methods

2.1. Patients

The medical records of consecutive patients with SRD who were diagnosed as having active PCP and treated with SMX/TMP as initial regimen at Division of Rheumatology, Department of Internal Medicine, Nagoya City University Hospital from January 2004 through October 2017; Department of Rheumatology, Seirei Hamamatsu General Hospital and Department of Infectious diseases and Rheumatology, Seirei Mikatahara General Hospital from January 2006 through October 2017 were reviewed.

Demographic data, clinical characteristics, comorbidities, and prior immunosuppressive therapy at the diagnosis of PCP; vital signs, degree of oxygen saturation, laboratory data including plasma β-D glucan, radiographic findings at the diagnosis of PCP. After starting treatment for PCP; survival, *anti*-pneumocystis medications and adjunctive glucocorticoids, required respiratory support, such as positive pressure ventilations with intubation or mask and oxygen supplementation, Intensive Care Unit admission, subsequent prevention measures for PCP and relapse of PCP evaluated for six months after starting PCP treatment were collected from medical charts and evaluated.

The classification of PCP for enrollment of this study was retrospectively assessed using the following diagnostic criteria for PCP. Patients who simultaneously had all of the following three items are classified as having PCP; (i) clinical manifestations of least one of the following, fever, cough, or dyspnea (ii) radiographic signs suggestive of PCP, such as patchy or ground-glass opacities with central, peripheral, or upper lobe predominance, (iii) abnormally elevated plasma β-D glucan or positive results of microscopic examination for *Pneumocystis jirovecii* or its DNA by polymerase chain reaction in sputum or bronchoalveolar lavage (BAL) fluid. The measurement of serum β-D-glucan levels was performed either with the β-D-glucan test WAKO (Wako Pure Chemical Industries, Osaka, Japan) or with the FUNGITEC G test MK II (Nissui Pharmaceutical, Tokyo, Japan). There are some reports regarding the cut-off for β-D-glucan level for the diagnosis of PCP [19,20]. In the current study, we defined values of at least 11 pg/mL (β-D-glucan test WAKO; n = 31) or 20 pg/mL (Fungitec G test MKII; n = 62) as the cut-off for abnormally elevated plasma β-D glucan test. All the chest radiographs and/or the computed tomography at the initiation of treatment for PCP were collected and evaluated by an expert radiologist (NK) for inclusion or exclusion of this study without clinical information. As for severity of PCP, we categorized the patients into two groups, severe and non-severe, by the degree of hypoxemia at the time of starting SMX/TMP therapy with the cut-off alveolar-arterial O2 gradient value of 45 mmHg [5]. Sequential organ failure assessment (SOFA) score at the time of starting SMX/TMP therapy was also assessed [21].

This retrospective study was approved by the institutional review board and ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki and the 2017 Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Written informed consent was waived because of the retrospective design of this study and information on the right to opt out of the study was presented.

2.2. Grouping of patients with different initial doses of SMX/TMP

According to the initial body weight-adjusted dose of SMX/TMP therapy, we divided our patients into the following three groups; the low-, ≤10 mg/kg/day; the intermediate-, >10 and <15 mg/kg/day; and the high-dose group, ≥15 and ≤ 20 mg/kg/day for TMP; and compared effectiveness and safety of SMX/TMP therapy between the three different initial dosage groups. We excluded the patients with prophylactic dose (equal to or less than 1 tablet/day or 2 tablets/once every two days) and those who received more than upper limit of the recommended dose range (>20 mg/kg/day for TMP) from the analyses for effectiveness and safety due to concerns for excessive rates for treatment modification and adverse events.

According to the package insert of SMX/TMP tablet in Japan, the dose of SMX/TMP should be reduced by 50% if creatinine clearance (CCr) calculated according to the Cockcroft and Gault formula is 15–30 mL/min, and SMX/TMP should not be administered for patients with PCP if CCr was less than 15 mL/min [6]. Thus if CCr was 15–30 mL/min at the diagnosis of PCP, patients were classified with the doubled amount of the actually prescribed doses of SMX/TMP, and if CCr was less than 15 mL/min, patients were excluded in this study.

2.3. Outcomes

The study endpoints were the rate of recovery from PCP; the 30-day survival rate; treatment modification, including changing the

dose of SMX/TMP from the initial dosage and switching to other *anti*-PCP drugs before recovery from PCP, and death by PCP despite the initial dose of SMX/TMP; and adverse events. We defined recovery from PCP as resolution of clinical signs and symptoms of PCP and successful attenuation or successful discontinuation of *anti*-PCP agents. Duration of the initial dosage for SMX/TMP and treatment with therapeutic dose of SMX/TMP were compared between the groups. Adverse drug reactions (ADRs) that emerged or worsened during SMX/TMP therapy were classified according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or death-related to adverse (grade 5) [22]. We defined CTCAE Grade $\geq$3 ADRs as severe ADRs in this study. Grades for blood and lymphatic system disorders, presented as bone marrow suppression (neutropenia, anemia, thrombocytopenia), gastrointestinal disorders (nausea, vomiting), abnormalities of transaminases (increased aspartate aminotransferase, alanine aminotransferase), and serum electrolyte abnormalities (hyponatremia, hyperkalemia) were applied for the greatest value of items in each category. Treatment-limiting ADRs were defined as documented toxicity of the SMX/TMP leading to termination of SMX/TMP therapy.

2.4. Statistical analyses

Missing data for PaO_2 and arterial partial pressures of carbon dioxide ($PaCO_2$) were imputed with the calculated PaO2 value from the peripheral oxygen saturation (SpO_2) using the oxygen dissociation curve and uniformly 35 mmHg, respectively [23,24].

In comparisons between two groups, we used the Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. To assess dose-dependent trends in dichotomous variables and continuous variables between three groups, we used the Cochran-Armitage trend test and the Jonckheere-Terpstra test, respectively. The cumulative probability of patients with continuation of SMX/TMP was calculated using the Kaplan–Meier method and the comparison between the groups were performed using the log-rank test and log-rank trend test, respectively. For multiple comparison, significance thresholds were corrected by Bonferroni method.

Multivariate logistic regression analysis was used to model the relationship between the following endpoints, treatment modification within 14 days and severe ADRs, and explanatory covariates. We used stepwise backward/forward regression selecting each explanatory variable based on the lowest Akaike information criterion, Bayesian information criterion, and backward selection based on P-value. The Receiver-operating-characteristic (ROC) curve analysis was also performed to explore discriminating ability of initial SMX/TMP dose for these endpoints and the optimal SMX/TMP dose cut-points were determined by Youden index. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [25].

3. Results

3.1. Patient demographics and clinical characteristics

Out of 93 SRD patients who developed PCP reviewed, 81 patients included in this study (Fig. 1). Patients who received *anti*-PCP agents other than SMX/TMP as the initial agent (n = 3) and SMX/TMP with over 20 mg/kg/day for TMP (n = 9) were excluded. Outcomes of the nine patients who received SMX/TMP with over 20 mg/kg/day for TMP were documented in the Supplementary Materials.

Demographics and clinical characteristics of patients in the three groups at the diagnosis of PCP are shown in Table 1. No patients complicated with HIV infection or malignancy. There were no patients who received SMX/TMP for PCP prophylaxis prior to inclusion of this study. Two patients with CCr of 15–30 mL/min who actually received SMX/TMP with the dose of 7.6 and 7.7 mg/kg/day for TMP were allocated to the high-dose group. There were no patients with CCr was less than 15 mL/min or on hemodialysis. All but two patients had elevated plasma β-D glucan levels. These two patients with negative β-D glucan test did not have concomitant interstitial lung disease and appropriately responded to SMX/TMP therapy.

There were significant dose-dependent decreasing trends in body weight, symptom treatment interval, and CCr; and significant dose-dependent increasing trends in the maximal dose of glucocorticoids per body weight for the treatment of PCP and proportion of patients receiving oxygen supplementation $\geq$5 L/min. Numerically more patients received methylprednisolone pulse therapy in higher SMX/TMP dosage groups. On the other hand, we could not find significant SMX/TMP dose dependent trend for severity scores

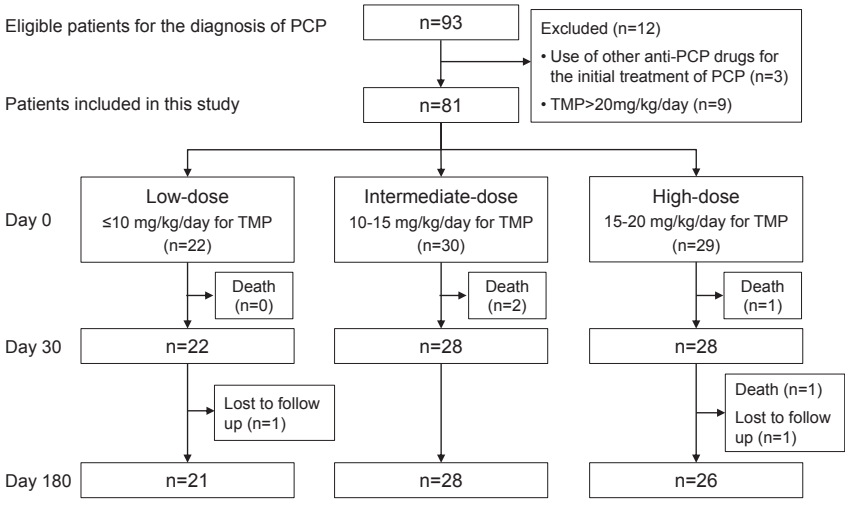


Fig. 1. Abbreviations: PCP, pneumocystis pneumonia; SMX, sulfamethoxazole; TMP, trimethoprim.

Table 1
Patient characteristics at baseline.

Clinical characteristics	Low-dose (n = 22)	Intermediate-dose (n = 30)	High-dose (n = 29)	*P*-value
Age (years old)	67.0 [35.0, 82.0]	64.0 [30.0, 86.0]	66.0 [36.0, 85.0]	0.78
Female gender (%)	68.2	70.0	82.8	0.14
Body weight (kg)	58.0 [32.2, 120]	51.2 [32.4, 84.0]	45.3 [37.8, 58.5]	<0.001
Patients with interstitial lung disease (%)	27.3	36.7	41.4	0.26
Systemic Rheumatic disease (%)				
Rheumatoid arthritis	72.7	66.7	62.1	
Systemic lupus erythematosus	4.5	3.3	6.9	
Dermatomyositis, polymyositis	9.1	23.3	6.9	
Mixed connective disease	4.5	0.0	0.0	
Microscopic polyangitis	0.0	3.3	3.4	0.76[a]
Adult onset still disease	4.5	3.3	3.4	
Giant cell disease	4.5	0.0	3.4	
Sjögren's syndrome	0.0	0.0	3.4	
Cryoglobulinemic vasculitis	0.0	0.0	6.9	
Hospital site (n)				
Nagoya City University Hospital	16	11	12	0.10[a]
Seirei Hamamatsu General Hospital	5	13	12	
Seirei Mikatahara General Hospital	1	6	5	
Prior GC treatment (PSL equivalent, mg/kg/day)	0.06 [0.00, 0.69]	0.07 [0.00, 1.62]	0.12 [0.00, 1.06]	0.17
Prior immunosuppressive drug use (%)	90.9	86.7	93.1	0.78
Prior biologic DMARD therapy (%)	42.9	36.7	31.0	0.44
Symptom treatment interval (days)	6.0 [0.0–27.0]	4.0 [0.0–15.0]	4.0 [0.0–12.0]	0.04
Lactate dehydrogenase (U/L)	313 [210, 539]	372 [241, 835]	327 [223, 1005]	0.06
White blood cell count ($\times 10^3$/l)	7.0 [3.3, 12.9]	6.9 [4.1, 14.6]	7.9 [1.5, 19.4]	0.69
Neutrophil count ($\times 10^3$/l)	5.4 [1.9, 9.0]	5.6 [2.3, 11.6]	6.5 [1.4, 17.5]	0.31
Lymphocyte count ($\times 10^3$/l)	0.8 [0.3, 3.8]	0.9 [0.3, 3.1]	0.9 [0.1, 4.6]	0.96
Hemoglobin (g/dl)	11.9 [8.6, 14.3]	12.3 [6.5, 16.2]	11.1 [7.3, 14.6]	0.1
Platelet count ($\times 10^9$/l)	220 [35, 486]	210 [54, 616]	241 [41, 477]	0.56
Aspartate aminotransferase (U/l)	29 [9, 66]	34 [11, 125]	30 [13, 151]	0.27
Alanine aminotransferase (U/l)	17 [7, 147]	22 [10, 90]	21 [5, 59]	0.61
Sodium (mEq/l)	138 [134, 142]	136 [129, 145]	138 [125, 144]	0.16
Potassium (mEq/l)	4.1 [3.3, 4.6]	4.3 [3.5, 4.7]	4.2 [3.4, 5.2]	0.40
Creatinine (mg/dl)	0.62 [0.40, 1.63]	0.70 [0.20, 1.23]	0.68 [0.27, 1.47]	0.83
Creatinine clearance (mL/min)	74.7 [42.7, 194]	75.9 [37.7, 214]	60.8 [20.3, 138.0]	0.04
Patients with creatinine clearance 15–30 mL/min (n)	0	0	2	0.10
C-reactive protein (mg/dL)	3.9 [0.60, 13.3]	4.9 [0.20, 23.3]	6.7 [0.04, 18.9]	0.06
Positive β-D glucan test	22/22 (100%)	28/30 (93.3%)	29/29 (100%)	0.88
Plasma β-D glucan (pg/mL)	58.2 [15.3, 383]	53.0 [11.3, 770]	62.6 [18.8, 3920]	0.16
Positive microscopic study on respiratory samples	0/0 (0%)	1/4 (25%)	0/4 (0%)	0.29
Positive PCR test for *Pneumocystis jirovecii*	6/13 (46.2%)	8/21 (38.1%)	17/26 (65.4%)	0.15
SMX/TMP (fold of one strength dose per day)	6 [4, 6]	9 [6, 12]	9 [4, 12]	<0.001
TMP (mg/kg/day)	7.7 [4.0, 10.0]	12.7 [10.1, 14.9]	16.4 [15.0, 20.0]	<0.001
Patients with increased GC treatment for PCP (%)	77.3	63.3	72.4	0.78
Maximal GC dose (PSL equivalent, mg/kg/day)	0.59 [0.15, 1.36]	0.95 [0.00, 2.47]	1.43 [0.00, 2.56]	<0.001
mPSL pulse therapy (%)	13.6	23.3	34.5	0.09
Oxygen Supplementation ≥5 L/min (%)	9.1	30.0	44.8	0.006
A-aDO_2 mmHg (%)	38.7 [15.0, 373.4]	43.8 [4.4, 514.8]	50.2 [15.0, 348.7]	0.15
Severe hypoxemia (%)	45.5	50.0	62.1	0.23
SOFA score	2.0 [1.0, 4.0]	2.0 [1.0, 8.0]	2.0 [1.0, 5.0]	0.20

Patients with PCP with hypoxemia were categorized into two groups; severe (alveolar-arterial O2 gradient (A-aDO_2) ≥45 mmHg) and non-severe (A-aDO_2 <45 mmHg).
Values are presented as median [minimum, maximum], otherwise specified.
P-values were determined by Cochran-Armitage trend test for dichotomous variables and the Jonckheere-Terpstra test for continuous variables, except for proportion of patients with systemic rheumatic disease and hospital site.
Abbreviations: DMARD, disease modifying antirheumatic drug; GC, glucocorticoid; mPSL, methylprednisolone; PCR, polymerase chain reaction; PSL, prednisolone; SMX, sulfamethoxazole; TMP trimethoprim.; A-aDO_2, alveolar-arterial O_2 gradient. SOFA, Sequential Organ Failure Assessment.
[a] *P*-value were determined by chi-square test.

for respiratory and multiple organ failure, as well as significant difference of these severity scores between the low-dose group and either the intermediate and the high-dose group.

3.2. Effectiveness and safety

Table 2 shows the treatment outcomes of patients with PCP in the three groups. Out of 81 patients, 78 recovered from PCP and the other three died without recovery from PCP. The recovery rate from PCP and the 30-day survival rate were identical for each group and similar between groups; 100%, 93.3%, and 96.7%, in the low-, the intermediate- and the high-dose group, respectively (Table 2).

Three patients died without recovery from PCP and one died after recovery from PCP. The clinical courses of them and patients who recovered from PCP were documented in the Supplementary Materials.

All patients experienced at least one grade 1 ADR during treatment period. Fig. 2A shows proportions of patients whose maximal grade in these ADRs were grade 2 and grade 3 or more, and those with treatment-limiting ADRs due to SMX/TMP in the three groups. There were significant dose-dependent increasing trends in proportions of patient experienced severe ADRs of grade 3 or more. Numerically more patients experienced treatment-limiting ADRs in higher dose groups. No patients experienced grade 5 ADRs in this study.

Table 2
Treatment outcome of patients with PCP in the different SMX/TMP dosage groups.

	Low-dose (n = 22)		Intermediate-dose (n = 30)		High-dose (n = 29)		*P*-value for trend
Patients recovered from PCP[a]	22	(100%)	28	(93%)	28	(97%)	0.58
Patients with 30-day survival	22	(100%)	28	(93%)	28	(97%)	0.58
Duration of initial dose of SMX/TMP therapy (days)	12.5 [5.0–21.0]		8.0 [3.0–21.0]		10.0 [3.0–21.0]		0.06
Duration of therapeutic SMX/TMP therapy (days) [b]	13.0 [5.0–22.0]		11.0 [5.0–23.0]		11.0 [3.0–53.0]		0.04
Patients required treatment modification[c]	9	(41%)	20	(67%)	19	(66%)	0.09
Dose increment of SMX/TMP	0	(0%)	2	(7%)	0	(0%)	
Dose reduction of SMX/TMP	3	(14%)	6	(20%)	5	(17%)	
Alternative therapy required	7	(32%)	14	(47%)	16	(55%)	
Pentamidine	4	(18%)	4	(13%)	9	(31%)	
Atovaquone	3	(14%)	10	(33%)	7	(24%)	
Ventilation support or ICU admission (%)	0	(0%)	3	(10%)	4	(14%)	0.09
Number of death in observation period	0	(0%)	2	(7%)	2	(7%)	0.28
Relapse of PCP within 180 days	0	(0%)	1	(3%)	1	(3%)	0.45

Abbreviations: PCP, pneumocystis jirovecii pneumonia; SMX, sulfamethoxazole; TMP, trimethoprim; ICU, Intensive care unit.
[a] Patients recovered from PCP at the final observation of treatment period irrespective of subsequent therapy.
[b] Therapeutic dose is defined by the dose more than prophylactic dose (equal to or less than 1 tablet/day or 2 tablets/once every two days).
[c] Treatment modification is defined by any dose change of SMX/TMP from the initial dosage and switching to other *anti*-PCP drugs before recovery from PCP, and death by PCP despite the initial dose of SMX/TMP.

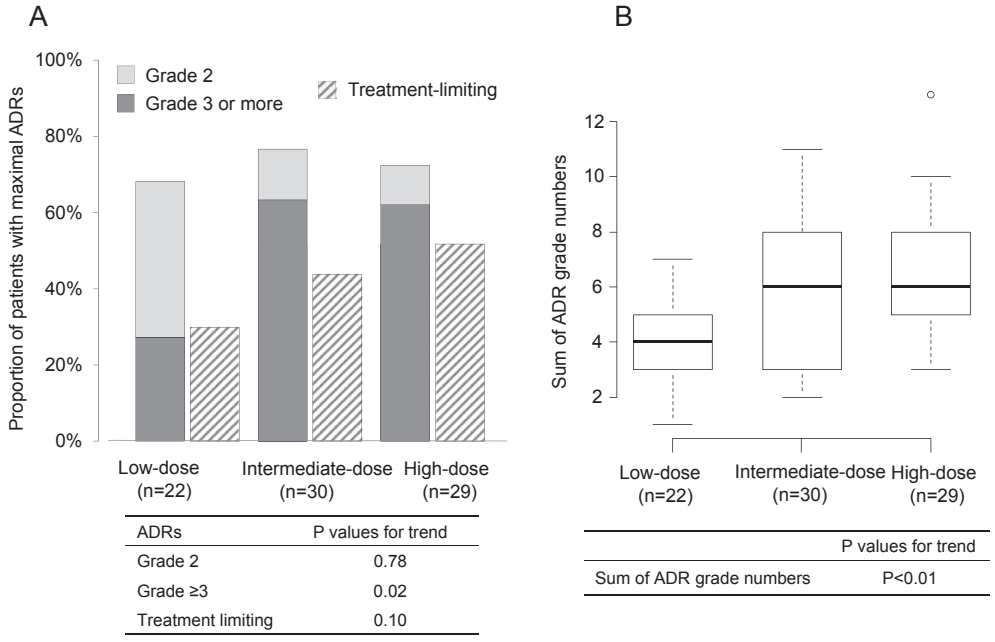


Fig. 2. (A) Proportion of patients whose maximum grade in these adverse drug reactions (ADRs) observed was grade ≥2 or grade ≥3 defined by Common Terminology Criteria for Adverse Events Version 4.0 and proportion of patients with treatment-limiting ADR were compared between different dosage groups. Treatment-limiting ADRs were defined as documented toxicity of the SMX/TMP leading to termination of SMX/TMP therapy. (B) Sum of each ADR grade numbers of fever, erythema multiforme, increased serum creatinine, and each of the maximum grade numbers of items regarding blood and lymphatic system disorders, including decreased neutrophil count, anemia, decreased platelet count, gastrointestinal disorders, including nausea, vomiting, abnormalities of transaminases, including increased aspartate aminotransferase, increased alanine aminotransferase, and electrolyte abnormalities, including hyponatremia, hyperkalemia in each patient were compared between the different dosage groups. Abbreviations: SMX, sulfamethoxazole; TMP, trimethoprim.

Fig. 2B shows that sum total of each ADR grade number of fever, erythema multiforme, increased creatinine, blood and lymphatic system disorders, gastrointestinal disorders, abnormalities of transaminases, and electrolyte abnormalities for each patients were compared between groups. There was significant dose-dependent increasing trends in the sum of ADR grade number for SMX/TMP ($P < 0.01$). In each of the ADR types analyzed was shown in Table 3. Significant dose-dependent trend for SMX/TMP was observed in bone marrow suppression mainly due to anemia ($P < 0.01$ in all grades, $P = 0.04$ in grade ≥3). However, maximal changes in hemoglobin levels during SMX/TMP treatment were not significantly different among the three groups.

Fig. 3 shows the Kaplan-Meier curve demonstrating the time to treatment modification and the time to severe ADRs graded as ≥3 in the three groups (Fig. 3). Although dose-dependent decreasing trends in time to treatment modification was not observed ($P = 0.07$), there were dose-dependent decreasing trends in time to severe ADRs ($P = 0.008$). The time to severe ADRs in the low-dose group was significantly longer than the other groups, but those in the intermediate and the high-dose groups were similar (Fig. 3B). Table 4 shows treatment outcome and ADRs of patients with PCP in the different SMX/TMP dosage groups stratified by hypoxemic status. Rates of 30-day survival in the three dosage groups were similar in the both strata and significant SMX/TMP dose-dependent

Table 3
Prevalence of individual types of adverse drug reactions stratified by severity.

Adverse drug reactions, n (%)	Low-dose (n = 22)		Intermediate-dose (n = 30)		Hight-dose (n = 29)		*P*-value for trend		*P*-value for low versus intermediate and high	
	All	Grades ≥ 3	All	Grades ≥ 3	All	Grades ≥ 3	All	Grades ≥ 3	All	Grades ≥ 3
Fever	2 (9%)	0 (0%)	3 (10%)	0 (0%)	4 (14%)	0 (0%)	0.58	NA	1	NA
Erythema multiforme	8 (36%)	4 (18%)	9 (30%)	7 (23%)	10 (34%)	7 (24%)	0.92	0.63	0.79	0.77
Increased serum creatinine	17 (77%)	0 (0%)	21 (70%)	0 (0%)	23 (79%)	1 (3%)	0.81	0.24	1	1
Δcreatinine (mg/dl)	0.16 [−0.50, 0.60]		0.10 [−0.16, 1.10]		0.20 [−0.20, 0.90]		0.72		0.76	
Gastrointestinal disorders	4 (18%)	0 (0%)	9 (30%)	5 (17%)	10 (34%)	4 (14%)	0.21	0.15	0.27	0.11
Nausea	4 (18%)	0 (0%)	9 (30%)	5 (17%)	10 (34%)	4 (14%)	0.21	0.15	0.27	0.11
Vomiting	1 (5%)	0 (0%)	1 (3%)	0 (0%)	5 (17%)	0 (0%)	0.09	N.A	0.67	N.A
Bone marrow suppressions	4 (18%)	0 (0%)	12 (40%)	0 (0%)	14 (48%)	3 (10%)	**0.03**	**0.04**	**0.04**	0.56
Decreased neutrophil count	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	1	NA
Δneutrophil count ($\times 10^9$/l)	2.29 [−2.97, 9.30]		4.71 [−2.92, 8.71]		5.63 [−13.2, 11.8]		0.21		0.26	
Anemia	2 (9%)	0 (0%)	8 (27%)	0 (0%)	13 (45%)	3 (10%)	**<0.01**	**0.04**	**0.03**	0.56
Δhemoglobin (g/dl)	0.25 [−1.9, 1.7]		0.3 [−2.9, 4.0]		0.0 [−2.3, 1.5]		0.3		0.49	
Decreased platelet count	3 (14%)	0 (0%)	5 (17%)	0 (0%)	4 (14%)	0 (0%)	0.99	NA	1	NA
Δplatelet ($\times 10^9$/l)	1.8 [−17.3, 26.8]		5.1 [−21.0, 26.0]		2.6 [−17.9, 24.5]		0.95		0.91	
Liver function abnormalities	9 (41%)	1 (5%)	19 (63%)	3 (10%)	20 (69%)	1 (3%)	**0.05**	0.8	**0.05**	1
Increased AST	4 (18%)	0 (0%)	12 (40%)	1 (3%)	13 (45%)	0 (0%)	0.06	0.91	0.07	1
ΔAST (U/l)	−3 [−28, 64]		−3 [−47, 323]		−1 [−73, 15]		0.66		0.46	
Increased ALT	11 (50%)	1 (5%)	18 (60%)	3 (10%)	20 (69%)	1 (3%)	0.17	0.8	0.31	1
ΔALT (U/l)	6 [−26, 214]		9 [−23, 216]		13 [−14, 117]		0.38		0.35	
Serum electrolyte abnormalities	17 (77%)	1 (5%)	26 (87%)	11 (37%)	27 (93%)	11 (38%)	0.1	**0.01**	0.16	**<0.01**
Hyponatremia	17 (77%)	1 (5%)	26 (87%)	10 (33%)	24 (83%)	8 (28%)	0.65	0.07	0.51	**0.02**
Δsodium (mmol/l)	−4.0 [−19.0, 5.0]		−5.0 [−32.0, 4.0]		−5.0 [−23.0, 4.0]		0.13		0.2	
Hyperkalemia	5 (23%)	0 (0%)	7 (23%)	3 (10%)	12 (41%)	3 (10%)	0.13	0.18	0.59	0.18
Δpotassium (mmol/l)	0.5 [−0.9, 1.9]		0.6 [−0.1, 2.1]		0.8 [−0.8, 2.1]		0.35		0.45	

P-values less than 0.05 are shown in bold.
Grades of adverse drug reactions were classified according to Common Terminology Criteria for Adverse Events Version 4.0.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; NA, not assessed.

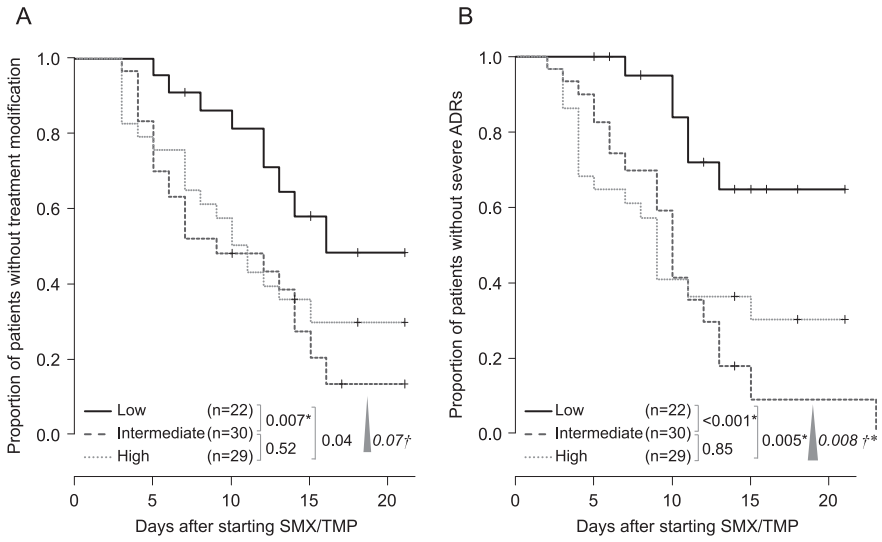


Fig. 3. Treatment modification was defined by changing the dose of SMX/TMP from the initial dosage or switching to other *anti*-PCP drugs before recovery from PCP. Severe ADRs were defined by CTCAE Grade ≥3 ADRs [22]. Unadjusted P-values were estimated by log-rank tests between each pair of the three groups. Asterisk indicated significant difference. Significance thresholds were corrected by Bonferroni method. †P-value presented by italic fonts were estimated by log-rank trend test. Abbreviations: ADRs, adverse drug reactions; SMX, sulfamethoxazole; TMP, trimethoprim.

trends for occurrence of treatment modification and time to treatment modification were not observed (Table 4, Fig. 4). On the other hand, significantly fewer patients experienced severe ADRs compared with higher dose groups and time to severe ADRs in the low-dose group was significantly longer than those in the intermediate- and the high-dose group (Fig. 4).

As the concomitant glucocorticoid therapy may affect the effectiveness and safety of SMX/TMP therapy for the treatment of PCP, we evaluated the 30-day survival, subsequent ICU admission or ventilator support, and severe ADRs in the two groups classified by the median split of the initial dose of concomitant glucocorticoid therapy. However, there were no significant difference between high- and low-glucocorticoid groups in total patients and in each of the three SMX/TMP dosing groups in terms of the 30-day survival, subsequent ICU admission or ventilator support, and severe ADRs.

Multivariate logistic regression analyses using three different variable selection methods consistently demonstrated that the

Table 4
Treatment outcome and ADRs of patients with PCP in the different SMX/TMP dosage groups stratified by hypoxemic status.

	Low-dose group (n = 22)	Intermediate-dose group (n = 30)	High-dose group (n = 29)	P value for trend[a]	All groups	P value[b]
30-day survival						
Non-severe hypoxemia	12/12 (100%)	14/15 (93%)	11/11 (100%)	0.97	37/38 (97%)	1
Severe hypoxemia	10/10 (100%)	14/15 (93%)	17/18 (94%)	0.56	41/43 (95%)	
Patients with treatment modification within 14 days						
Non-severe hypoxemia	1/12 (8%)	10/15 (67%)	5/11 (46%)	0.06	16/38 (42%)	0.08
Severe hypoxemia	7/10 (70%)	7/15 (47%)	13/18 (72%)	0.70	27/43 (63%)	
Patients with severe ADRs						
Non-severe hypoxemia	5/12 (42%)	7/15 (47%)	5/11 (46%)	0.85	17/38 (45%)	0.19
Severe hypoxemia	1/10 (10%)	12/15 (80%)	13/18 (72%)	0.004	26/43 (61%)	

Patients with PCP were stratified into two groups according to hypoxemic status, severe (alveolar-arterial O2 gradient (A-aDO2) ≥45 mmHg) and non-severe (A-aDO2 <45 mmHg) [5]. Severe ADRs were defined by CTCAE Grade ≥3 ADRs [22].
Abbreviations: ADRs, adverse drug reactions.
[a] *P*-value for SMX/TMP dose-dependent trend of proportions of patients who reached the endpoints.
[b] *P* value for proportions of patients in all SMX/TMP dose group who reached the endpoints with non-severe hypoxemia and severe hypoxemia.

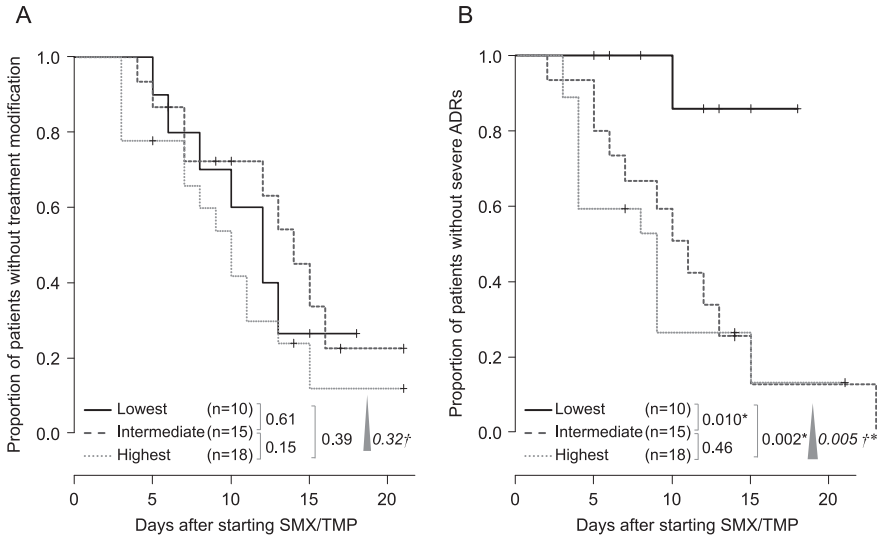


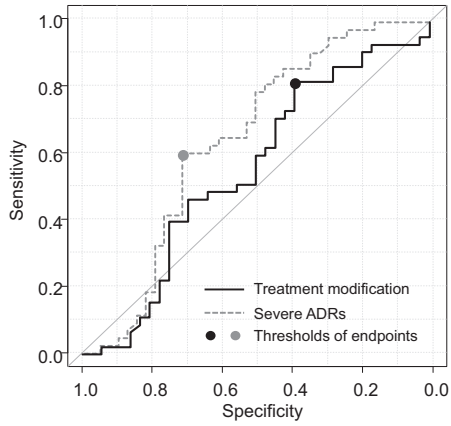
Fig. 4. Severe hypoxemia was defined A-aDO2 ≥45 mmHg. Treatment modification was defined by changing the dose of SMX/TMP from the initial dosage or switching to other *anti*-PCP drugs before recovery from PCP. Severe ADRs were defined by CTCAE Grade ≥3 ADRs [22]. Unadjusted P-values were estimated by log-rank tests between each pair of the three groups. Asterisk indicated significant difference. Significance thresholds were corrected by Bonferroni method. †P-value presented by italic fonts were estimated by log-rank trend test. Abbreviations: ADRs, adverse drug reactions; SMX, sulfamethoxazole; TMP, trimethoprim.

low-dose group was independently and negatively associated with treatment modification within 14 days and severe ADRs (Table 5, Supplemental Table 1). Treatment modification within 14 days was not significantly associated with severe hypoxemia. Fig. 5 shows the area under the ROC curves for discrimination of patients with treatment modification and severe ADRs with SMX/TMP dose. Only the area under the ROC curves for discrimination of patients with severe ADRs with SMX/TMP dose differed significantly from 0.5 and SMX/TMP dose of 13.85 mg/kg for TMP might be a critical point for increasing ADRs.

Table 5
Factors associated with treatment modification and occurrence of severe ADRs after starting SMX/TMP therapy.

Variable	β	standard error	Wald χ^2	P-value	Odds ratio	95% CI
Treatment modification within 14 days						
(Intercept)	0.57	0.45				
Treatment for PCP with higher GC dose	−0.84	0.59	2.08	0.15	0.43	[0.14 to 1.35]
Severe hypoxemia	0.90	0.53	2.91	0.09	2.46	[0.88 to 6.91]
The low-dose group for SMX/TMP	−1.41	0.60	5.55	0.02	0.24	[0.08 to 0.79]
Severe ADRs						
(Intercept)	0.52	0.27				
The low-dose group for SMX/TMP	−1.50	0.55	7.47	0.01	0.22	[0.08 to 0.65]

The following covariate were used in this analysis: age older than 65 years, female gender, higher body weight by the median split (threshold of 49 kg by the median split), presence of concomitant interstitial lung disease, presence of severe hypoxemia (A-aDO_2 ≥45 mmHg) at the time of starting PCP treatment, the low-dose group for initial SMX/TMP dose, higher maximal glucocorticoid dose for the treatment of PCP (threshold of 0.94 mg/kg/day of prednisolone equivalent by the median split). Stepwise backward/forward regression selecting each explanatory variable based on the lowest Akaike information criterion was used. Severe ADRs were defined by CTCAE Grade ≥3 ADRs [22].
Abbreviations: A-aDO_2, alveolar-arterial O_2 gradient; ADRs, adverse drug reactions; CI, confidence interval; GC, glucocorticoids; PCP, pneumocystis pneumonia; SMX, sulfamethoxazole; TMP trimethoprim.



Endpoint	AUC	[95%CI]	Threshold*	Specificity	Sensitivity
Treatment modification	0.55	[0.42-0.69]	10.11	0.39	0.82
Severe ADRs	0.64	[0.52-0.77]	13.85	0.71	0.61

Fig. 5. *Thresholds were given by SMX/TMP dose (mg/kg/day for TMP). Abbreviations: AUC, area under the curve; ADRs, adverse drug reactions; SMX, sulfamethoxazole; TMP, trimethoprim.

4. Discussion

The results of our retrospective observational study regarding different SMX/TMP dosage for the treatment of PCP in patients with non-HIV-infected SRD patients revealed the following three points. First, although substantial percentages of patients required treatment modification in all three groups, the recovery and survival rates of the low-dose group were comparable to higher dose groups, including conventional standard dose regimen. Second, the low-dose group was significantly associated with less treatment modification within 14 days and lower burden of severe ADRs compared to the intermediate- and the high-dose groups. Third, there were no difference in regarding prevalence of treatment modification and ADRs between the intermediate- and the high-dose groups. Furthermore, ROC analysis demonstrated that SMX/TMP dose of 13.85 mg/kg/day for TMP might be a critical point for increasing the risk of severe ADRs.

Although some physicians reported the effectiveness of the lower dose SMX/TMP therapy [14–17], effectiveness of further reduced-dose regimen less than 10 mg/kg/day for TMP as an initial treatment regimen for adult patients with PCP remains to be elucidated.

Recently, Nakashima et al. reported the results of consecutive 24 patients diagnosed non HIV PCP treated with low-dose TMP-SMX (TMP, 4–10 mg/kg/day) while comparing historical control treated with conventional-dose SMX/TMP (TMP, 10–20 mg/kg/day). The low-dose group showed excellent survival rates with higher completion rate of the initial regimen compared to the historical conventional high-dose group [18].

However, these retrospective studies comprise critical selection bias regarding underlying diseases. In the current study, the target population was solely patients with SRDs and recovery rate and the 30-day survival rate in the low-dose SMX/TMP therapy (TMP 7.7 [4.0, 10.0] mg/kg/day) was comparable to inter-mediate and high-dose therapy, which was consistent with previous studies.

Previous studies have consistently shown that lower dose SMX/TMP regimen decreased prevalence of adverse events compared to the conventional high-dose regimen. Kosaka et al. reported that severe adverse events in the low-dose groups (TMP <15 mg/kg) was significantly lower than that of conventional dose group (TMP, 15–20 mg/kg) [17]. Bowden et al. reported that PCP patients who treated with TMP at 10 mg/kg- SMX 50 mg/kg had significantly lower prevalence of these events than those with TMP at 20 mg/kg-SMX 100 mg/kg [16]. Nakashima et al. also reported that the total adverse reaction rate in the low-dose group (TMP 4–10 mg/kg/day) was lower than the conventional-dose group (TMP 10–20 mg/kg/day) [18]. Consistent with these studies, the severe ADRs of low-dose SMX/TMP therapy (TMP 7.7 [4.0, 10.0] mg/kg/day) were significantly lower than the other groups in the current study.

Previous studies reported that increased serum creatinine levels, hyponatremia, hyperkalemia, anemia, and neutropenia considered as dose-dependent ADRs, and erythema multiforme, fever, gastrointestinal disorders, liver function abnormalities, and thrombocytopenia were as dose-independent ADRs [29,30]. In the current study, significant dose-dependent increasing trends were observed in bone marrow suppression mainly due to anemia. We also analyzed the rates of and the times to dose-dependent and dose-independent severe ADRs after starting SMX/TMP among three groups (Supplemental Table 2 and Supplemental Fig. 1). There were decreasing trends in the rates of and the time to dose-dependent severe ADRs. These trends were not observed in dose-independent severe ADRs.

This study comprises several limitations mainly due to its study design. First, due to non-randomized design of this study, there are selection bias and indication bias and we cannot draw definitive conclusion as to the equal effectiveness or non-inferiority of lower dose SMX/TMP regimen compared to the high-dose conventional regimen. Second, there were no predefined observation and treatment protocols in this study and judgment for switching to alternative therapy was solely dependent on treating physician's discretion. Third, the results of this study cannot generalizable to patients with SRD who developed PCP with severe respiratory failure or multiple organ damage because only a few patients requiring ventilator support were included in this study. Forth, inclusion criteria might be less specific in comparison with previous studies. Positive microscopic tinctorial test of respiratory samples is very specific, but not sensitive for diagnosing PCP, especially in non-HIV patients. The most studied populations in the previous PCP studies in the non-HIV patients were classified as having PCP without microscopic tinctorial criterion but with other bacteriological criteria such as PCR test for *Pneumocystis jirovecii* DNA or an increased plasma β-D-glucan level [1,15,17,18,31,32]. Indeed, prevalence of the “definitive PCP” which requires positive result of microscopic tinctorial analysis was only 6.7–9.5% of total studied population in the previous studies [1,31,32]. To increase the specificity of selection criteria for PCP, some studies applied double positive for β-D glucan test and PCR test as a bacteriological criterion [17], others applied clinical criterion, such as “appropriate response to the standard treatments for PCP” [1,31,32]. Due to the design of this study and the current state that PCR test for *Pneumocystis jirovecii* DNA has been not covered by National Health Insurance. In the present study, implementation rate for PCR test was 74%. In addition, this study evaluated the effectiveness of lower dose SMX/TMP therapy in comparison with the standard dose regimen. Thus, the criteria for PCP used in this study should not include the clinical response criteria and would inevitably be more inclusive compared to the PCP criteria in the previous studies that included the criterion for the clinical response to the standard treatments for PCP.

In conclusion, the low dose SMX/TMP therapy might have comparable effectiveness and was associated with less treatment modification and lower burden of severe ADRs compared to the intermediate and the high-dose SMX/TMP therapy in SRD patients with PCP. The results observed here warrants further investigation of optimal dosage of SMX/TMP therapy in such a clinical setting in randomized control trials.

Disclosure statement

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

Author contributions

All authors were involved in collecting patient data in each involved institution. SO and TN drafted the article and all authors approved the final version of this article. NK reviewed the all chest imagings of all patients. Statistical analysis was performed by SO. TN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2018.11.014.

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