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ORIGINAL RESEARCH

Efficacy and Safety of Low-Dose Trimethoprim-Sulfamethoxazole (TMP-SMZ) for the Prevention of *Pneumocystis jirovecii pneumonia* (PJP) in Non-HIV, Non-Transplant Immunosuppressed Patients: A Real-World Cohort Study

Dakui Cao[1], Juanfen Mo[2], Haiqin Wang[1], Jianping Jiang[1], Mengqing Cao[1], Ziyi Zhu[1], Hua Zhou[3]

[1]Department of Respiratory and Critical Care Medicine, The Second Hospital of Jiaxing, Jiaxing, Zhejiang Province, 314000, People's Republic of China; [2]Central Laboratory, The Second Hospital of Jiaxing, Jiaxing, Zhejiang Province, 314000, People's Republic of China; [3]Department of Respiratory Medicine, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, 310003, People's Republic of China

Correspondence: Hua Zhou, Department of Respiratory Medicine, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310003, People's Republic of China, Email zhouhua1@zju.edu.cn

Purpose: To evaluate the noninferiority and safety of low-dose trimethoprim-sulfamethoxazole (TMP-SMZ, 200/40 mg qd) with respect to conventional-dose TMP-SMZ in preventing *Pneumocystis jirovecii pneumonia* (PJP) in non-human immunodeficiency virus (HIV), non-transplant, immunosuppressed patients.

Methods: This retrospective cohort study included patients who received PJP-preventing therapy at the First Affiliated Hospital of Zhejiang University School of Medicine from April 2021 to December 2023. The patients were divided into low-dose group (TMP-SMZ 200/40 mg qd, n=57) and conventional-dose group (400/80 mg qd, n=65). The primary endpoint was the 90-day incidence of PJP, and the secondary endpoints included all-cause mortality and adverse drug events (assessed on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 and Kidney Disease: Improving Global Outcomes (KDIGO) criteria).

Results: No patients in either group developed PJP within 90 days (risk difference (RD) = 0, 95% confidence interval (CI): −0.05 to 0.05). There was no statistically significant difference in the incidence of adverse reactions (ARs), such as hematologic toxicity (granulocytopenia: 5.26% vs 1.54%, p=0.339), liver injury, and kidney injury, between the low-dose group and the conventional-dose group. The median survival time was 193 days in the low-dose group vs 130 days in the conventional-dose group (p=0.312).

Conclusion: In non-HIV, non-transplant, immunosuppressed patients, the efficacy of low-dose TMP-SMZ (200/40 mg/d) in the prevention of PJP was not inferior to that of conventional-dose TMP-SMZ, and the safety profiles of the two doses were equivalent.

Keywords: trimethoprim-sulfamethoxazole, *Pneumocystis jirovecii* pneumonia, immunosuppression

Introduction

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic lung infection caused by the bacterium P. jirovecii that mainly affects immunocompromised patients,[1] including patients with or without human immunodeficiency virus (HIV) infection. In recent years, the marketing of various novel immunosuppressive drugs has led to a significant increase in the incidence of PJP in non-HIV, non-transplant immunocompromised patients,[2] with other studies revealing that the mortality rate associated with PJP (17.2–52.9%) in non-HIV patients is significantly higher than that in HIV patients (6.7%).[3,4]

How can PJP be prevented in clinical practice? Currently, for cancer patients and patients who have undergone solid organ or haematopoietic cell transplantation, the relevant guidelines[5] propose trimethoprim-sulfamethoxazole (TMP-SMZ) at recommended dosages of 15–20 mg/kg/d TMP and 75–100 mg/kg/d SMZ as first-line treatment for preventing PJP in both non-HIV and HIV patients.[6] Although some studies have offered guidance and recommended prevention strategies for

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non-HIV patients,[7] these prevention strategies have not been extensively investigated. Some studies have recommended that for the prevention of PJP, non-HIV immunosuppressed patients should receive TMP-SMZ as 2 tablets per day at 800/160 mg or three tablets per week or one tablet per day at 400/80 mg;[8] however, at these doses, adverse drug events, including drug-induced rashes and gastrointestinal, liver, and dose-dependent kidney and blood diseases, are common in clinical practice, which makes continuing treatment at these doses difficult. Some studies have used low-dose (200/40 mg) and conventional-dose TMP-SMZ (400 mg/80 mg) to prevent PJP in HIV and kidney transplant patients,[9–12] revealing no significant differences in adverse reactions (ARs) or survival rates between the two groups. However, prospective evidence of the optimal preventative dose is lacking in non-HIV, nontransplant immunosuppressed patients. Is it possible to use low-dose TMP-SMZ to prevent the development of PJP in these patients?

Therefore, this study retrospectively analysed the use of 1 tablet per day (400 mg/kg) of TMP-SMZ for immunosuppression among outpatients and inpatients admitted to the Department of Respiratory and Critical Care Medicine of the First Affiliated Hospital of Zhejiang University School of Medicine, China, from April 2021 to December 2023. The primary endpoint was the incidence of PJP within 90 days, and secondary endpoints included all-cause mortality and the incidence of ARs.

Materials and Methods

Study Protocol

This study was developed with a prospective-retrospective cohort design (April 2021-December 2023) and is reported in accordance with the STROBE reporting standard. Approval for the study was obtained from the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (approval number: 2024-yan-1011, IIT20240549B), who waived the need for informed consent. As a retrospective cohort study, it solely involves the retrospective analysis of existing patient medical records, posing no additional risks to patients' rights and interests. All medical records in question are anonymized data generated during routine clinical diagnosis and treatment, with no means to identify specific individuals. For these reasons, the Ethics Committee determined that patient informed consent was not required for this study and issued a corresponding waiver of consent, which aligns with the action mentioned earlier of waiving the need for informed consent.

Furthermore, this study strictly complies with the principles outlined in the Declaration of Helsinki. Stringent confidentiality measures have been implemented throughout the collection, collation, analysis, and storage of all patient data to ensure the protection of patients' personal privacy and data security. All personnel involved in the study have signed data confidentiality agreements, stipulating that relevant data may only be used within the scope of this research and must not be disclosed to any third party.

Study Subjects

The inclusion criteria were as follows: (i) age 18–75 years; (ii) regular follow-up; (iii) no prior transplantation and no infection with HIV; (iv) immunosuppression due to causes such as treatment for previous malignant tumours and long-term high-dose hormone use (>20mg of equivalent prednisone per day for more than 1 month); and (v) immunosuppression from other causes necessitating PJP prevention. The exclusion criteria were as follows: (i) nonadherence to the prescribed TMP-SMX regimen (as reflected in inconsistencies between the medication records in the database and the patient's description) and an inability to determine the actual medication status; (ii) lack of regular follow-up or loss to follow-up; (iii) current treatment for PJP; (iv) death from other causes; (v) active PJP infection; (vi) TMP-SMX contraindications; (vii) an eGFR<30 mL/min/1.73 m^2; and (viii) pregnancy.

Study Groups

Patients were divided into groups according to the actual medication status. The low-dose group consisted of patients treated with TMP-SMX 200/40 mg qd (n=57); the conventional-dose group consisted of patients treated with TMP-SMX 400/80 mg qd (n=65). The baseline characteristics of the patients in the two groups were balanced with propensity score matching (PSM). The matched variables included age, sex, underlying disease, immunosuppressant type, and lymphocyte count.

Adverse Drug Reactions

Anaemia (according to the WHO standards): mild: haemoglobin (Hb) 90–110 g/L; moderate: Hb 60–90 g/L; severe: Hb <60 g/L. Liver injury (according to the Council for International Organizations of Medical Sciences (CIOMS) criteria): serum alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN) or alkaline phosphatase (ALP) ≥ 2 ×ULN. Kidney injury (according to the Kidney Disease: Improving Global Outcomes (KDIGO) criterion):[13] acute kidney injury (AKI) stage 1: serum creatinine 1.5–1.9 times the baseline value, or ≥0.3 mg/dL, within 48 hours or a decrease in urine output by 0.5 mL·kg-1·h-1 for more than 6 hours; AKI stage 2: serum creatinine 2.0–2.9 times the baseline value and a decrease in urine output by 0.5 mL·kg-1·h-1 over 12 hours; AKI stage 3: serum creatinine 3 times the baseline value or the need for replacement therapy and a decrease in urine output by 0.5 mL·kg-1·h-1 for more than 24 hours or no urine for more than 12 hours. Thrombocytopenia (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0 criteria): Grade 1: platelet count (PLT) 75–100×109/L; Grade 2: PLT 50–75×109/L; Grade 3: PLT of 25–50×109/L; Grade 4: PLT <25×109/L; Grade 5: death due to thrombocytopenia. Granulocytopenia (NCI-CTCAE 4.0 criteria): mild: 1000–1500/μL or (1–1.5)×109/L; moderate: 500–999/μL or (0.5–0.99)×109/L; severe: 200–499/μL or (0.2–0.49)×109/L; extremely severe: <200/μL or <0.2×109/L.

The baseline evaluation included a complete blood count (including lymphocyte count, neutrophil count, PLT, and Hb levels), liver function (ALT, AST, and ALP levels), renal function (serum creatinine levels), and chest computed tomography (CT). Follow-up examinations were performed at 1, 3, and 6 months after the drug was first administered and at discontinuation of the drug.

Statistics

Among the quantitative data, continuous variables are expressed as the mean ± standard deviation, discrete variables are expressed as the median (upper quartile, lower quartile), and Sex was dichotomized as male or female with results reported as percentages. Among the baseline characteristics, categorical variables were compared with the chi-square test, *t* test, or Fisher's exact test. For comparisons between two groups, the independent samples *t* test was used when the variances were homogeneous, and a nonparametric test was used when the variances were not homogeneous. The paired *t* test was used to compare data in the same group before and after treatment, and confounding factors, such as age and underlying diseases, were adjusted for with Cox regression. A two-sided P <0.05 was considered to indicate statistical significance. All analyses were performed in SPSS 23 software.

Results

The primary outcome of this study was the incidence of PJP and patient survival during the 90-day follow-up period following the start of PJP prevention treatment.

1. Baseline characteristics of the study subjects:

A total of 57 patients were included in the low-dose group, and 65 patients were included in the conventional-dose group. The mean age of the patients in the low-dose group was 66 (58.5, 73.5) years, and the mean age of the patients in the conventional-dose group was 68 (60.5, 74) years; the difference between the groups was not significant (P=0.253). In the low-dose group, there were 41 males, accounting for 71.9%, and 16 females, accounting for 28.1%. In the conventional-dose group, there were 44 males, accounting for 67.7%, and 21 females, accounting for 32.3%. The sex distribution between the groups was not significant (P=0.613) (Table 1).

In terms of coexisting underlying diseases, patients in two groups presented with neoplastic diseases (including malignant lung tumours, haematological tumours, breast tumours, gynaecological tumours, otolaryngological tumours, and digestive system tumours), connective tissue disease-related interstitial lung disease (CTD-ILD), other systemic autoimmune diseases, allergic alveolitis, organizing pneumonia, idiopathic eosinophilia, and interstitial pneumonia. The proportions of patients with these diseases were not significantly different between the groups (P > 0.05 for all comparisons). In particular, the treatments for benign diseases, such as connective tissue disease-related interstitial lung disease, other systemic autoimmune diseases, allergic alveolitis, organizing pneumonia, idiopathic eosinophilia, and interstitial pneumonia, all met the criteria for preventing PJP, ie, prednisone or an equivalent drug at a dose ≥20 mg and a duration > 4 weeks. There was no significant difference between the two groups in the prevalence of these diseases (P=0.272) (Table 2).

Table 1 Baseline Characteristics of the Patients in the Two Groups

Item	Low-dose Group (n=57)	Conventional-dose Group (n=65)	P value
Age (years)	66 (58.5,73.5)	68 (60.5,74)	0.253
Sex			
Male,%	41 (71.9)	44 (67.7)	0.613
Female, %	16 (28.1)	21 (32.3)	
Comorbidities,%			
Malignant lung tumours	24 (42.1)	23 (35.4)	0.272
Haematological tumours	7 (12.3)	4 (6.2)	
Breast tumour	0	1 (1.5)	
Gynaecological tumours	2 (3.5)	0	
Digestive system tumours	2 (3.5)	3 (4.6)	
Ear, nose and throat tumours	0	1 (1.5)	
CTD-ILD	11 (19.3)	19 (29.2)	
Other systemic autoimmune diseases	1 (1.8)	0	
Allergic alveolitis	1 (1.8)	2 (3.1)	
Organizing pneumonia	3 (5.3)	4 (6.2)	
Idiopathic eosinophilia	1 (1.8)	0	
Interstitial pneumonia	5 (8.8)	8 (12.3)	
Lymphocyte count ($\times 10^9$/L)	0.6 (0.41,0.89)	0.56 (0.37,1.04)	0.967
TMP-SMZ treatment duration (days)	46 (40,59)	32 (20,60)	0.153

Table 2 Use of Immunosuppressants in Benign Diseases

Disease	Type of Immunosuppressant	Number of Patients in the Low-dose Group	Number of Patients in the Conventional-Dose Group
CTD-ILD	Methylprednisolone	11	19
	Tacrolimus	5	2
	Mycophenolate mofetil	3	5
	Hydroxychloroquine	1	1
	Cyclophosphamide	0	1
	Tripterygium vine	0	1
Other systemic autoimmune diseases	Methylprednisolone	1	0
Allergic alveolitis	Methylprednisolone	1	2
Organizing pneumonia	Methylprednisolone	3	4
Idiopathic eosinophilia	Methylprednisolone	1	0
Interstitial pneumonia	Methylprednisolone	5	8

The lymphocyte count in the low-dose group was 0.6 (0.41, 0.89)×109/L, whereas that in the conventional-dose group was 0.56 (0.37, 1.04) ×109/L. There was no significant difference in the lymphocyte count between the two groups (P=0.967). The duration of TMP-SMZ administration was 46 (40, 59) days in the low-dose group and 32 (20, 60) days in the conventional-dose group, and there was no statistically significant difference between the two groups (P=0.153) (Table 1).

2. In the low-dose group, the lymphocyte count was 0.6 (0.41, 0.89) ×109/L before treatment and 1.59 (0.88, 2.32) ×109/L 1 month after treatment; the difference was significant (P=0.001). In the conventional-dose group, the lymphocyte count was 0.56 (0.37, 1.04) ×109/L before treatment and 1.74 (1.07, 2.48) ×109/L 1 month after treatment; similar to the low-dose group, the difference was significant (P=0.001) (Table 3).

Table 3 Change in the Lymphocyte Count in the Two Groups Before and After Treatment

Groups	Before treatment	After treatment	P value
Low-dose group ($\times 10^9$/L)	0.6 (0.41, 0.89)	1.59 (0.88, 2.32)	0.001
Conventional-dose group ($\times 10^9$/L)	0.56 (0.37, 1.04)	1.74 (1.07, 2.48)	0.001

3. ARs in the two groups

Incidence: There was no significant difference between the low-dose group and the conventional-dose group in the incidence of ARs such as granulocytopenia, thrombocytopenia, anaemia, liver injury, and kidney injury. The incidences of specific ARs in the low-dose group vs the conventional-dose group were as follows: granulocytopenia, 5.26% vs 1.54%; thrombocytopenia, 21.05% vs 23.08%; anaemia, 75.44% vs 67.69%; liver injury, 12.28% vs 10.77%; and kidney injury, 5.26% vs 4.62% ($P > 0.05$ for all comparisons).

Severity: There was no significant difference between the two groups of patients in terms of the severity of granulocytopenia, thrombocytopenia, or anaemia. Specifically, there was no difference in the distribution of mild, moderate, or severe granulocytopenia between the two groups ($P = 0.75$); there was no difference in the distribution of Grade 1, 2, 3, and 4 thrombocytopenia between the two groups ($P = 0.33$); there was no significant difference in the distribution of mild, moderate, and severe anaemia between the two groups ($P = 0.426$); and there was no significant difference in the distribution of AKI stage 1 or 2 between the groups ($P = 0.80$) (Tables 4 and 5).

Table 4 Incidence of ARs in the Two Groups of Patients

Groups	Granulocytopenia	Thrombocytopenia	Anaemia	Liver Injury	Kidney Injury
Low-dose group (n=57), %	3 (5.26)	12 (21.05)	43 (75.44)	7 (12.28)	3 (5.26)
Conventional-dose group (n=65), %	1 (1.54)	15 (23.08)	44 (67.69)	7 (10.77)	3 (4.62)
χ^2		0.72	0.89	0.07	0
P	0.339	0.788	0.345	0.794	1.0

Table 5 Severity of ARs in the Two Groups

Item	Low-dose Group (n=57)	Conventional-dose Group (n=65)	P value
Granulocytopenia, %			
Mild	2 (3.51)	1 (1.54)	0.75
Moderate	0	0	
Severe	1 (1.75)	0	
Thrombocytopenia, %			
Grade 1	5 (8.77)	7 (10.77)	0.33
Grade 2	6 (10.53)	3 (4.62)	
Grade 3	0	3 (4.62)	
Grade 4	1 (1.75)	2 (3.08)	
Anaemia, %			
Mild	26 (45.61)	32 (49.23)	0.426
Moderate	14 (24.56)	9 (13.85)	
Severe	3 (5.26)	3 (4.62)	
Kidney injury, %			
Stage 1	2 (3.5)	2 (3.08)	0.80
Stage 2	1 (1.75)	1 (1.54)	
Stage 3	0	0	

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Table 6 Baseline Values and Maximum Changes in ARs in the Two Groups

Groups	Item	Baseline Value	Maximum Change	P value
Low-dose group (n=57)	Lymphocyte count (×10^9/L)	0.6 (0.41, 0.89)	1.59 (0.88, 2.32)	0.001
	PLT count (×10^9/L)	218 (133, 308.5)	167 (111.5, 202.5)	0.001
	Neutrophil count (×10^9/L)	6.89 (4.58, 9.50)	3.80 (2.54, 6.20)	0.001
	Hb (g/L)	119.3±19.25	106.55±23.76	0.001
	ALT (U/L)	22 (15, 38)	39 (27.5, 73.79)	0.001
	ALP (U/L)	81 (63.5, 98.98)	103 (70, 149)	0.001
	Serum creatinine (μmol/L)	67 (54.5, 82.5)	78 (61, 97)	0.001
Conventional-dose group (n=65)	Lymphocyte count (×10^9/L)	0.56 (0.37, 1.04)	1.74 (1.07, 2.48)	0.001
	PLT count (×10^9/L)	180 (125.5, 260)	170 (113, 220)	0.001
	Neutrophil count (×10^9/L)	7.2 (4.83, 9.47)	4.5 (2.66, 6.10)	0.001
	Hb (g/L)	120.34±18.70	109.71±24.34	0.001
	ALT (U/L)	23 (12.5, 43)	47 (20, 90)	0.001
	ALP (U/L)	72 (56, 95.5)	73 (61.5, 106.5)	0.223
	Serum creatinine (μmol/L)	66 (55, 79)	73 (63, 88.5)	0.001

4. Changes in ARs during treatment between the two groups

In the low-dose group, the lymphocyte count and ALT, ALP, and serum creatinine levels all increased over the course of treatment (P=0.001). In contrast, the PLT count, neutrophil count, and Hb level decreased over the treatment course (P=0.001).

In the conventional-dose group, the lymphocyte count, ALT level, and serum creatinine level all increased over the course of treatment (P=0.001). In contrast, the PLT count, neutrophil count, and Hb level decreased over the course of treatment (P=0.001). Although the ALP level also decreased over the treatment course, the change was not significant (P=0.223) (Table 6, Figures 1 and 2).

5. The survival time of the low-dose group was 193 (87.5, 352.5) days, and that of the conventional-dose group was 130 (45.5, 344.5) days; there was no significant difference between the two groups (P = 0.312). During the 90-day follow-up period, none of the patients in either group developed PJP. Kaplan–Meier analysis revealed that there was no significant difference in survival time between the two groups (P>0.05). Cox regression analysis revealed that the conventional-dose group had a hazard ratio (HR) of 0.501 (95% CI: 0.176–1.422, P = 0.194) compared with the low-dose group, indicating no significant difference in survival risk between the two groups. (Figure 3).

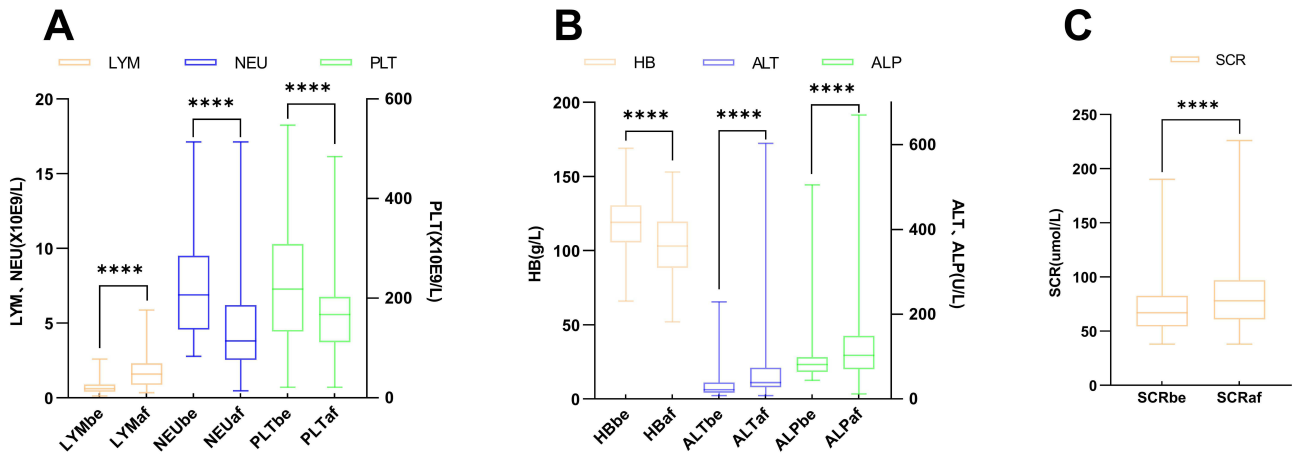

Figure 1 Shows the baseline values of and maximum changes in lymphocyte, neutrophil, and platelet (PLT) counts, as well as hemoglobin (Hb), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum creatinine levels in the low - dose group. In this figure, subfigure (**A**) represents the changes in serum creatinine in the low - dose group; subfigure (**B**) represents the changes in lymphocytes, neutrophils, and platelets in the low - dose group; subfigure (**C**) represents the changes in Hb, ALT, and ALP in the low - dose group. **** indicates a significant difference.

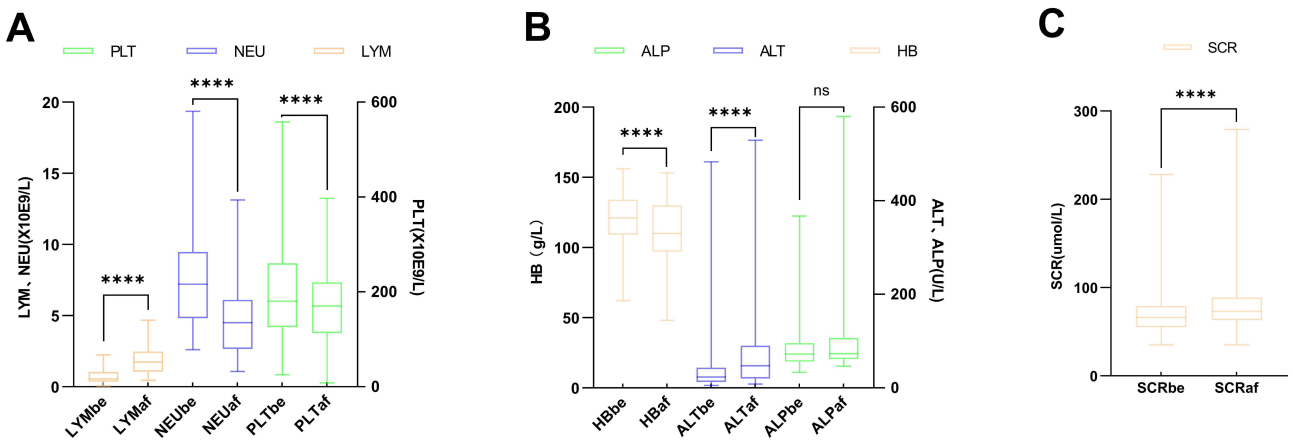

Figure 2 Shows the baseline values of and maximum changes in lymphocyte, neutrophil, and platelet (PLT) counts, as well as hemoglobin (Hb), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum creatinine levels in the conventional - dose group. In this figure, subfigure (**A**) represents the changes in lymphocytes, neutrophils, and platelets in the conventional - dose group; subfigure (**B**) represents the changes in Hb, ALT, and ALP in the conventional - dose group; subfigure (**C**) represents the changes in serum creatinine in the conventional - dose group. **** indicates a significant difference, and ns indicates no significant difference.

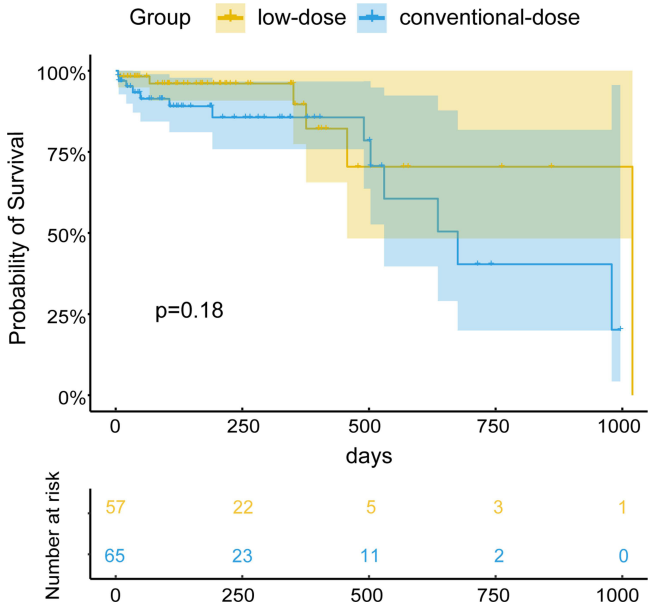

Figure 3 Analysis of the survival time of the two groups (P>0.05). Kaplan-Meier survival curves for patients in the low-dose and conventional-dose groups. Cox regression analysis revealed that the conventional-dose group had a hazard ratio (HR) of 0.501 (95% confidence interval [CI]: 0.176–1.422, P = 0.194) compared with the low-dose group, indicating no significant difference in survival risk between the two groups.

Discussion

This study aimed to evaluate the effects of different doses of TMP-SMZ (0.5 tablets/day vs 1 tablet/day) on preventing PJP in non-HIV, non-transplant immunosuppressed patients. In this retrospective study, the control group received one tablet of TMP-SMZ per day, while the experimental group received half a tablet of TMP-SMZ per day.

First, no significant differences were found between the two groups in terms of age, sex distribution, underlying diseases (such as tumours and CTD-ILD), and duration of medication, indicating good comparability between the groups. Under these circumstances, the results of this study indicated that, in terms of preventing PJP, there was no significant difference between the group who received 0.5 tablets/day of TMP-SMZ and the group who received 1.0 tablets/day of TMP-SMZ, and neither group developed PJP. The results of this study suggest that in the non-HIV, non-transplant immunosuppressed population, the effect of low-dose TMP-SMZ (200/40 mg/d) on the prevention of PJP was not inferior to that of conventional-dose TMP-SMZ (400/80 mg/d).

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In addition, this study evaluated the ARs of the two groups of patients during treatment with TMP-SMZ. The results revealed that the incidence and severity of five Ars (granulocytopenia, thrombocytopenia, anaemia, liver injury, and kidney injury), did not significantly differ between the two groups, indicating that increasing the drug dose did not increase the risk of ARs. This finding is very important for clinical practice, as a lower dose of TMP-SMZ can be used to prevent PJP, reducing unnecessary medical costs without sacrificing efficacy. In a systematic review and meta-analysis, Butler-Laporte et al[14] reported that the mortality associated with trimethoprim at a dose of 15 mg/kg/d in the treatment of PJP was similar to that associated with the conventional dose, while the incidence of serious adverse events was significantly reduced. In children who had undergone solid organ transplantation, a low dose of TMP-SMZ (2.5 mg/kg/d) effectively prevented the development of PJP,[10] and the incidence and severity of ARs were reduced accordingly. In a study involving adult renal transplant patients, some scholars reported that the use of 0.25 tablets of TMP-SMZ (200/40 mg) once every other day effectively prevented the development of PJP, and no significant ARs were observed. In immunosuppressed populations without HIV infection, one study[9] showed that a low dose of TMP-SMZ (8.71 mg/kg/d) could be used to prevent the development of PJP without inducing significant adverse reactions. As can be seen from these findings, in existing studies on the use of low-dose TMP-SMZ for the prevention of PJP, the dose used differs depending on the disease. However, the optimal TMP-SMZ dose for preventing PJP and achieving a minimal incidence of ARs for each disease remains to be verified with additional clinical studies.

This study used the peripheral lymphocyte count instead of the traditional CD4+T lymphocyte count as an indicator in the prevention of PJP. In non-HIV immunocompromised patients, a CD4+ T-cell count <200/mm3 is considered a sensitive biomarker for identifying the risk of PJP.[8] However, other studies have reported that[15,16] the CD4+ T lymphocyte count in PJP patients is much greater than 200 mm3. Some studies have reported[17] that the cut-off value for the CD4+ T lymphocyte count requiring chemoprevention should be far greater than the recommended value for HIV patients. Therefore, the academic community still remains divided regarding the cut-off value of the CD4+ T lymphocyte count. Peripheral lymphopenia is also considered a strong predictor of PJP.[17–19] Some studies have shown[20] that the peripheral blood lymphocyte count could be used as a parameter in a PJP prediction model. These findings indicate that the peripheral blood lymphocyte count can be used as a reference indicator for the prevention of PJP. Because this study did not determine the CD4+ T-cell count in the patients, the peripheral blood lymphocyte count was used instead.

Studies[21] have suggested that 2 weeks of prophylaxis is considered effective in preventing PJP in non-HIV patients. In this study, the duration of treatment was determined according to the immunosuppression status and clinical manifestations of the patients and the effective prevention of PJP. Studies[22] have suggested that the duration of PJP prophylaxis should be at least 21 days. However, following heart transplantation, some centres recommend only 6 months of PJP prophylaxis, whereas others recommend 12 months or even life-time use of the drug.[23] However, some scholars[8] believe that the duration of medication use should differ depending on the underlying diseases and cannot be generalized. More clinical studies are needed to further explore the optimal duration of preventative treatment in different states of different diseases.

This study also has several limitations. First, the limited sample size (n<100 for each group) may reduce the statistical power for the secondary endpoints (such as specific ARs); second, the retrospective design is associated with a risk of residual confounding bias; third, data on TMP-SMZ plasma concentrations are lacking; and finally, the short median follow-up time (<6 months) may have resulted in an underestimation of the long-term risk of PJP.

In view of the results of this study, future studies can focus on the following aspects. First, large-scale clinical trials should be conducted to verify the preventive effects of different doses of TMP-SMZ. Next, monitoring of the concentration of TMP-SMZ in the blood or alveoli should be considered, as it may answer the following questions: Can the plasma/alveolar concentration of TMP-SMZ guide the next steps in treatment? Which drug concentration yields the best specificity and sensitivity? Are different drug concentrations required for the treatment of different underlying diseases? With drug concentration monitoring, can the accuracy of the drug dose be further improved? Finally, the effects of TMP-SMZ in combination with other therapies should also be explored. A long-term follow-up study is needed to evaluate the long-term safety and survival benefits of the use of TMP-SMZ.

Conclusion

This study showed that over 90 days, both the low - dose TMP - SMZ (200/40 mg qd) group and the conventional - dose TMP - SMZ (400/80 mg qd) group had comparable safety, and no PJP cases were observed in either group. However, given the limitations of this study, long - term efficacy and the determination of the optimal dosing strategy for TMP - SMZ in the prevention of PJP require validation in larger - scale studies. These findings provide preliminary information for the application of TMP - SMZ, and future research should further explore the optimal use strategy to better guide clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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