Effectiveness and Safety Evaluation of Thrice Weekly Double Strength vs Daily Single Strength Trimethoprim-Sulfamethoxazole for Prophylaxis of Pneumocystis Jirovecii Pneumonia after Kidney Transplantation: A Two-Year Prospective Cohort Study

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ABSTRACT: Purpose: It is hard for clinicians to choose the best regimen for pneumocystis jirovecii pneumonia (PJP) prophylaxis. The aim is to evaluate the effectiveness and safety of thrice weekly double strength (TWDS) vs daily single strength (DSS) trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis of PJP after kidney transplantation. **Methods:** Adult renal transplant recipients (RTRs) who were transplanted between January 1, 2015 and July 1, 2018 were evaluated. A total of 189 RTRs were prescribed PJP prophylactic regimen during the study period (TWDS group: n=98; DSS group: n=91). **Results:** Morbidity due to PJP infection was significantly higher in TWDS group as compared with DSS group (8.60% vs 1.14%, p= 0.021). There was a significant trend toward higher prevalence of confirmed PJP (log‐rank=0.021) in TWDS group. The use of DDS TMP-SMX for prophylaxis after kidney transplantation was associated with a 79% reduction in the incidence of PJP comparing the prophylactic regimen of TWDS. There was no significant difference between the two groups in the overall rate of premature TMP-SMX discontinuation and laboratory indexes. **Conclusion:** Six months of DSS TMP-SMX prophylaxis was more effective than TWDS TMP-SMX regimen with the same safety profile.

INTRODUCTION

Pneumocystis jiroveci, formerly pneumocystis carinii, remains an important opportunistic fungal pathogen in renal transplant recipients (RTRs) (1). In the absence of effective prophylaxis, 5%‐15% solid organ transplant recipients may develop pneumocystis jirovecii pneumonia (PJP) post-transplant (2-3). Thus, the updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation recommends anti-pneumocystis prophylaxis for all solid organ transplant recipients (4). Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line agent for prevention of PJP, all other prophylactic agents (i.e., dapsone, atovaquone, pentamidine) should be considered second line agents due to drug intolerance, cost, and effectiveness issues.

TMP-SMX associates with numerous adverse drug reaction, including leukopenia, absolute neutropenia, thrombocytopenia, anemia, and hepatitis. Besides that, trimethoprim has the capacity to inhibit potassium and creatinine secretion resulting in hyperkalemia and elevation of serum creatinine (4). Post-transplant management, therefore, becomes a balancing act between preventing PJP on the one hand and managing the adverse effects of TMP-SMX on the other. Despite consensus about the significant role of TMP-SMX in routine post-transplant care, there remains a remarkable vagueness about how TMP-SMX should best be used for PJP prophylaxis as the dose, frequency and duration are inconsistent. Three guidelines suggested that TMP-SMX 80mg/400mg (single strength) daily or 160mg/800mg (double strength) three times weekly (4-6). And the British Transplantation Society only suggested that TMP‐SMX 80mg/400mg daily for PJP prophylaxis. The duration of PJP prophylaxis had been prolonged in recent years. Guidelines published before 2017 suggested that the duration of PJP prophylaxis is at least 4 months or 3‐6 months post-transplant (6-9). Guidelines published after 2017 suggested that the

duration of the PJP prophylaxis treatment should be 6‐12 months (4-5).

None of the guidelines are evidence-based and leave the decision to clinicians to prefer one dosing regimen over the other. Thus, the aim of this study is to evaluate the effectiveness and safety of thrice weekly double strength (TWDS) vs daily single strength (DSS) TMP-SMX for prophylaxis of PJP after kidney transplantation.

METHODS

Study design and patient population
This study was conducted over a two-year period at Chaoyang hospital in Beijing, China This was a prospective cohort study evaluating the effectiveness and safety of two strategies for prophylaxis of PJP (TWDS vs DSS) (Ethics Approval: 2019-7-2-1). Sodium bicarbonate has the capacity to promote TMP-SMX secretion reducing the risk of kidney injury according to the package insert. Hence, two tablets of sodium bicarbonate with one tablet of TMP-SMX were given to the patients at the same time. Adult renal transplant recipients (RTRs) transplanted between January 1, 2015 and July 1, 2018 were evaluated. Patients who received TWDS or DSS TMP-SMX for prevention of PJP for about 6 months post-transplant were eligible. All the patients were given either an interleukin-2 receptor antagonist or rabbit ant-thymocyte globulin (rATG) to ensure similar induction regimens. Tacrolimus (TAC), mycophenolate mofetil (MMF) and glucocorticoids were standard initial treatments to maintain immunosuppressive strategy and prevent allograft rejection in our center. Post-transplant laboratory monitoring is performed weekly for the first three months, once every two weeks for the next three months, and then monthly thereafter. Reasons for exclusion from this analysis included 1) patients received a multi-organ transplant, 2) the glomerular filtration rate of the patients were less than 30mL/min on discharge day, 3) patients did not follow-up.

Data collection
Inpatient/outpatient physical and electronic medical records, including laboratory data, clinic visit notes, and medication histories, were reviewed for demographics, laboratory values, immunosuppressive therapies, transplant characteristics, pathology reports, and allograft outcomes.

Outcomes
The effectiveness outcome was incidence of PJP (the diagnosis of PJP was confirmed based on microscopy with staining or a polymerase chain reaction). The safety outcomes were the early discontinuation rate of TMP-SMX and the incidence of laboratory abnormalities (hyperkalemia, defined as serum potassium $\geqslant 5.5$ mmol/L; total leukopenia, defined as total WBC $\leqslant$ 3000/cu mm; absolute neutropenia, defined as neutrophil count $\leqslant$ 500/cumm; thrombocytopenia, defined as platelet count $\leqslant$ 100,000/cu mm; anemia, defined as hemoglobin $\leqslant 100$ g/L. and hepatitis, defined as alkaline phosphatase $\geqslant$ 125 IU/mL, alanine aminotransferase $\geqslant$ 45 IU/mL, and/or aspartate aminotransferase $\geqslant$ 40 IU/mL).

Statistical analysis
Standard descriptive statistics were used to summarize the study population characteristics. The Fisher's exact or chi‐square tests for categorical variables and Student's t-test for continuous variables were used. Continuous variables were presented as the mean, with the standard deviation (SD). The overall morbidity was analyzed using KM curves. The log‐rank test was used to compare incidence of PJP between two groups throughout a period of 24 months. The y-axis represents the cumulative incidences of PJP between those two groups, with percentage as its unit. And the x-axis represents the time period we followed up, with month as its unit. A two‐sided test was performed and a P‐value < 0.05 was considered to be statistically significant. Univariable Cox proportional hazards regression was used to evaluate variables as a potentially protective factor for incidence of PJP. Data were analyzed using SPSS 25 statistical software.

RESULTS

A total of 189 RTRs were prescribed PJP prophylactic regimen during the study period (TWDS group: n=98; DSS group: n=91). Baseline demographics of the two groups were comparable (Table 1, p > 0.05). Duration of prophylaxis was the same between two groups (5.08 $\pm$ 1.85 vs 5.75 $\pm$ 3.04, p = 0.073). For the risk factors for PJP, there was no significant difference in 1-year and 2-year allograft rejection rate, but 1-year CMV infection rate was higher in the DSS group than the TWDS group (15.31% vs 32.97%, p=0.04, Table 1).

Incidence of PJP
The overall morbidity of PJP infection in the TWDS group was higher than that in the DSS group (8.60% vs 1.14%, p= 0.021). The 1-year incidence of PJP infection after transplantation was 7.53% in the TWDS group and 1.14% in the DSS group (P = 0.037), and the incidence of PJP infection occurring

Table 1. Baseline characteristics of total study subjects

Characteristic	TWDS group (n=98)	DSS group (n=91)	P value
Age(y)	41.38±10.72	41.80±11.47	0.79
Height(cm)	168.83±14.07	166.76±13.65	0.31
Weight(kg)	66.35±15.39	64.34±16.90	0.31
Gender,male(n,%)	70(71.43)	54(59.34)	0.08
Han people(n,%)	95(96.94)	90(98.90)	0.35
Smoking(n,%)	21(21.43)	16(17.58)	0.51
Alcohol consumption(n,%)	10(10.20)	10(1.10)	0.86
Comorbidity			
Hypertension(n,%)	83(84.69)	78(85.71)	0.84
Diabetes(n,%)	10(10.20)	5(5.49)	0.23
hyperlipemia(n,%)	1(1.02)	3(3.30)	0.28
hyperuricemia(n,%)	4(4.08)	3(3.30)	0.78
CHD(n,%)	0(0.00)	2(2.20)	0.14
Laboratory data			
Creatinine(umol/L)	860.60±266.94	831.83±270.34	0.46
Urea nitrogen(mmol/L)	21.43±9.10	21.74±8.06	0.81
TC(mmol/L)	4.33±1.82	4.45±1.03	0.58
LDL-C(mmol/L)	2.42±1.91	2.25±0.75	0.42
Leucocyte(*10^9/L)	7.22±2.71	6.94±2.06	0.43
Neutrophilic(%)	71.64±10.52	71.09±10.58	0.72
Lymphocytes(%)	19.52±8.97	19.75±8.09	0.85
Hemoglobin(g/L)	112.38±19.45	113.90±21.16	0.61
Induction drug after kidney transplantation			
ATJ(ramus)	5.09±2.63	4.76±2.04	0.50
Basiliximab(ramus)	1.92±0.28	1.93±0.26	0.79
Etiology of ESRD			
Glomerulonephritis (n,%)	27(27.55)	26(28.57)	0.88
Polycystic kidney (n,%)	4(4.08)	7(7.69)	0.29
Hypertensive nephropathy (n,%)	4(4.08)	5(5.49)	0.65
Tubal nephritis (n,%)	2(2.04)	0(0)	0.17
Diabetic nephropathy (n,%)	3(3.06)	3(3.30)	0.93
Other causes(n,%)	4(4.08)	7(7.69)	0.29
Unclear(n,%)	54(55.10)	43(47.25)	0.28
Risk factors for PJP			
1-year CMV infection rate (n, %)	15(15.31)	30(32.97)	0.04
2-year CMV infection rate (n, %)	1(1.02)	1(1.10)	0.96
1-year AR rate (n, %)	1(1.02)	1(1.10)	0.96
2-year AR rate (n, %)	0(0.00)	0(0.00)	/

TWDS, thrice weekly double strength; DSS, daily single strength; LDL-C=low density lipoprotein cholesterol, TC=total cholesterol, ATJ=Antithymocyte globulin, CHD=coronary artery heart disease, ESRD = end-stage renal disease, CMV=cytomegalovirus, AR=allograft rejection.

within the 12 months to 24 months after transplantation was 1.08% and 0.00%, respectively (p= 0.329). For patients withPJP, 47.06% have risk factors for pneumocystis pneumonia (30.77% vs 100%, p=0.029). The Kaplan-Meier curve showing time to development of PJP is in Figure 1. There was a significant trend toward higher prevalence of confirmed PJP in the TWDS group versus the DSS group by 24 months after transplantation (log‐rank=0.021). The use of DDS TMP-SMX for

prophylaxis after kidney transplantation was associated with a 79% reduction in the incidence of PJP (hazard ratio [HR] = 0.21; 95% CI = 0.06–0.79) comparing the prophylactic regimen of TWDS.
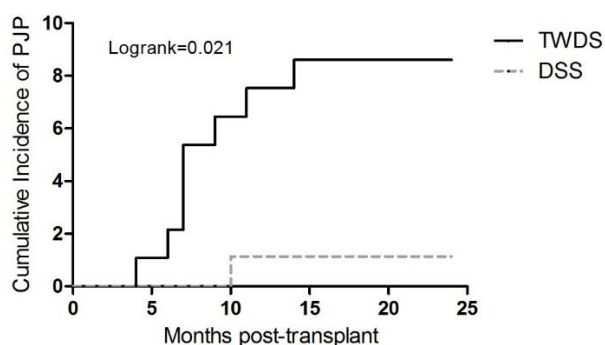

Figure 1. Cumulative incidence of pjp receiving TWDS or DSS.

Early discontinuation of TMP-SMX
Of the 8 patients who discontinued TMP-SMX early, 7 had documented reasons. Three patients experienced elevation of serum creatinine, one patient experienced leukopenia, the remaining 3 stopped taking the drugs themselves. The overall rate of premature TMP-SMX discontinuation was similar between the groups (5.1% vs 3.3%; P = 0.538, Table 2).

Laboratory abnormalities
There was no significant difference between the two groups in the laboratory indexes before taking TMP-SMX.. After taking TMP-SMX, no significant difference was found between the two groups in any laboratory indexes except the incidence of hyperkalemia (5.128% vs 0.00%, p=0.032, Table 3).

DISCUSSION
This was a prospective study evaluating the impact of two different 6-month prophylactic regimens of TMP-SMX, TWDS versus DSS, on the prevalence of PJP disease in 189 RTRs. Our findings suggested that six months of DSS TMP-SMX prophylaxis was more effective than TWDS TMP-SMX regimen with the same safety profile. And for all we know, this was the first clinical trial comparing TWDS to DSS TMP-SMX for six months in de-novo KTR during the past 30 years.

Routine anti-pneumocystis prophylaxis is generally recommended in most transplant centers. Our study demonstrated that six months of DSS TMP-SMX regimen was more effective than TWDS TMP-SMX regimen for PJP prophylaxis in RTRs. Our result was different from previous studies published in the 1980s (10-12). Three studies published in the 1980s found no difference in the rate of PJP infections after daily vs thrice-weekly prophylaxis. It might be due to different regimen of immunosuppressive agents. Increased understanding of immune rejection has led to the development of safe modern immunosuppressive agents. Along with the low incidence of post-transplant rejection, nonspecific side effects of immunosuppression include infection, particularly opportunistic infections increased (13). So more effective and safety prophylactic regimens for PJP is needed.

Now with widespread use of prophylaxis and changing immunosuppressant regimens, the incidence post-transplant is uncertain but appears to range from 0.3 to 2.5% (14-17). The overall morbidity of PJP infection in our studies was higher (4.97%) than previous published study. It might be due to the immunosuppressive regimen selected. Nowadays, induction therapy (either basiliximab or antithymocyte globulin) is widely used, and studies had demonstrated that induction therapy was associated with an increased risk of infection (18-19). It led to the increase of the morbidity of PJP infection. In addition, recent reports have shown that despite effective prophylaxis for 6-12 months post-transplantation, PJP may emerge (20). Risk factors include cytomegalovirus infection (CMV) and graft rejection (14). Most patients with PJP had risk factors for pneumocystis pneumonia in our study (30.77% and 100%, respectively). CMV infection rate was higher in DSS group than TWDS group. It might be due to increasing concerns about CMV infection. However, even the risk to get PJP infection was higher in DSS group, our study demonstrated that the use of DDS TMP-SMX for prophylaxis after kidney transplantation was associated with a 79% reduction in the incidence of PJP comparing the prophylactic regimen of TWDS.

The prophylactic duration had been prolonged in recent years. Guidelines recommended 6-12 months of PJP prophylaxis after transplantation, SOT patients remain at risk for PJP beyond complete course of prophylaxis (21). Goto et al recommended lifelong prophylaxis of kidney transplant recipients to prevent new outbreaks (22). Most patients suffering from PJP have risk factors of pneumocystis pneumonia. Extended prophylaxis targeting recipients with risk factors may reduce the incidence of PJP. Targeted prophylaxis may be more feasible.

Our study demonstrated that both TWDS and DSS were well-tolerated regimens for PJP prophylaxis in RTRs. The incidence of hyperkalemia was lower in the DSS group compared to the TWDS group in the first week after taking TMP-SMX. Then no significant difference between the two groups was found in the laboratory abnormalities. Only eight patients (4.23%) discontinued TMP-SMX before the

prescribed 6-month posttransplant mark in total in our study. Other published studies reported poor tolerability, as evidenced by higher discontinuation rates. Giullian et al used a dose of 1 single-strength tablet daily of TMP-SMX and reported a discontinuation rate of 40%. But the main reason for stopping TMP-SMX prematurely was drug hypersensitivity reaction (allergy, rash, or non-infectious fever) (n=16, 25%) (23). Sulfonamides is an essential drug for urinary tract infections in China, therefore most of the patients used TMP-SMX before. The doctors would not prescribe TMP-SMX for the patients who had a TMP-SMX allergy history. Hence, avoidance of antibiotic sulfonamides in patients with a history of a sulfonamide allergy is largely necessary, and this will decrease the discontinuation rate to a great extent. Mitsides and colleagues reported a discontinuation rate of 38% when using the same dose of 1 single-strength tablet of TMP-SMX once daily. Reported reasons for discontinuation included acute kidney injury, gastrointestinal symptoms, and leukopenia (24). In our prophylactic regimen, the patients were given one tablets of TMP-SMX with two tablets of sodium bicarbonate at the same time. Sodium bicarbonate has the capacity to promote TMP-SMX secretion reducing the risk of kidney injury according to the package insert. Besides that, asking the patients to drink more water after taking TMP-SMX is another effective way for risk reduction.

Limitations of this study include the fact that the data were collected at a single center. Both the DSS group and TWDS group had fewer patients for comparison. Second, pneumocystis colonization can also be a challenging problem in transplant recipients despite the use of TMP-SMX prophylaxis.

CONCLUSION

In summary, we demonstrated that six months of DSS TMP-SMX prophylaxis was more effective than a TWDS TMP-SMX regimen with the same safety profile. Further randomized controlled trial comparing DSS to TWDS TMP-SMX in RTRs is justified.

Table 2. Early discontinuation of TMP-SMX

	Elevation of serum creatinine (n,%)	Leukopenia (n,%)	Self-discontinuation (n,%)	Unknown (n,%)	Total (n,%)
TWDS group (n=98)	1 (1.02)	1 (1.02)	3 (3.06)	0 (0.00)	5 (5.10)
DSS group (n=91)	2 (2.20)	0 (0.00)	0 (0.00)	1 (1.10)	3 (3.30)
P	0.52	0.33	0.09	0.30	0.54

TWDS, thrice weekly double strength; DSS, daily single strength.

Table 3. Laboratory abnormalities after taking TMP-SMX

Characteristics	TWDS group	DSS group	P value
One day before taking TMP-SMX			
Serum level of creatinine (umol/L)	99.36±34.91	107.30±31.47	0.13
Hyperkalemia (n,%)	0(0.00)	0(0.00)	/
Total leukopenia (n,%)	0(0.00)	2(2.27)	0.18
Absolute neutropenia (n,%)	15(19.23)	21(23.86)	0.47
Thrombocytopenia (n,%)	3(3.85)	3(3.41)	0.88
Anemia (n,%)	43(55.13)	60(68.18)	0.08
ALT or AST (n,%)	11(14.86)	13(16.05)	0.84
One week after taking TMP-SMX			
Serum level of creatinine (umol/L)	107.80±35.13	113.28±31.95	0.29
Hyperkalemia (n,%)	4(5.13)	0(0.00)	0.03
Total leukopenia (n,%)	0(0.00)	2(2.27)	0.18
Absolute neutropenia (n,%)	15(19.23)	23(26.14)	0.29
Thrombocytopenia (n,%)	1(1.28)	2(2.27)	0.63
Anemia (n,%)	17(21.79)	31(35.23)	0.06
ALT or AST (n,%)	13(16.67)	15(17.05)	0.95

Table 3 continues…

One month after taking TMP-SMX

Serum level of creatinine (umol/L)	104.39±31.93	113.15±32.41	0.08
Hyperkalemia (n,%)	1(1.27)	2(2.30)	0.62
Total leukopenia (n,%)	1(1.27)	1(1.27)	0.95
Absolute neutropenia (n,%)	35(44.30)	37(42.53)	0.82
Thrombocytopenia (n,%)	1(1.27)	4(4.60)	0.21
Anemia (n,%)	8(10.13)	15(17.24)	0.19
ALT or AST (n,%)	3(3.40)	7(8.05)	0.25
Six month after taking TMP-SMX			
Serum level of creatinine (umol/L)	103.56±29.91	108.16±24.86	0.30
Hyperkalemia (n,%)	1(1.28)	0(0.00)	0.29
Total leukopenia (n,%)	2(2.56)	4(5.19)	0.50
Absolute neutropenia (n,%)	42(53.85)	48(63.16)	0.24
Thrombocytopenia (n,%)	3(3.85)	1(1.32)	0.26
Anemia (n,%)	2(2.56)	4(5.26)	0.50
ALT or AST (n,%)	6(7.69)	7(9.10)	0.75

TWDS, thrice weekly double strength; DSS, daily single strength; TMP-SMX, trimethoprim-sulfamethoxazole; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

CONFLICT OF INTEREST. The authors declare no conflicts of interest.

ETHICAL APPROVAL. This study was approved by the institutional review board of Hospital. (Ethics Approval: 2019-7-2-1)**.** This work was followed the Declarations of Helsinki and Declaration of Istanbul guidelines and that no executed prisoner was used as a donor. The table indicating the medical explanations for brain death of the donors in our study was provided in Supporting Table 1.

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